THE CLINICAL FEATURES AND DIAGNOSIS OF SPORADIC CREUTZFELDT-JAKOB DISEASE IN THE UNITED KINGDOM, 1990-2002

Sarah Cooper

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Abstract

Background

Sporadic Creutzfeldt-Jakob disease (sCJD) is an invariably fatal spongiform encephalopathy that has a worldwide incidence of approximately 1/1, 000000 per year. Prospective surveillance has been in place in the UK since 1990, coordinated by the National CJD Surveillance Unit (NCJDSU). Accurate surveillance of CJD is important not only in detecting changes in patterns of disease and predicting trends but also in instituting protective public health measures.

Aims of the study

To define circumstances where making a clinical diagnosis of sCJD is potentially problematic. To explore ways of improving diagnostic accuracy and enhancing surveillance in these settings.

Methodology

Clinically "atypical" cases of sCJD were defined according to specific criteria (young, long duration, certain focal features at onset) and identified by retrospective case-file review of all 485 pathologically-proven cases (1990-2002). Comparisons were made with a consecutively selected "Core group" of "typical" sCJD (n=133). Cases identified only at autopsy, cases finally classified as "Possible sCJD" (according to internationally agreed criteria) and initially suspect but pathologically proven non-cases were also identified and analysed.

Results and conclusions

Twenty four per cent of all pathologicallly confirmed sCJD cases were "atypical". For each "atypical" subgroup, relatively distinct phenotypic characteristics were identified when compared with the Core group. Long duration cases were associated with early depression and personality change, more psychiatric features and infrequent cerebellar or extrapyramidal features. Young cases had less ataxia at onset and more psychiatric symptoms and involuntary movements. Cases presenting with predominantly cerebellar features were associated with a higher prevalence of visual disturbance and sensory symptoms and a longer illness duration. Those with a pure visual onset had a shorter duration with less cerebellar or extrapyramidal features. Amongst "atypical" cases (with the exception of pure visual onset cases) the electroencephalogram was diagnostically less sensitive and where positive was associated with short disease duration and increased age at onset. Visual onset cases were associated with genotype MM at codon 129 of the prion protein gene. Nineteen per cent of sCJD cases were referred after autopsy, of these about one third were not diagnosed whilst alive. Alzheimer's disease (AD) was the most likely alternative diagnosis in pathologically proven non-cases except when disease duration was less than six months, where paraneoplastic/neoplastic disease was commonest. Diagnostic accuracy is likely to improve with a greater understanding of the range of disease presentation, evolution and differential diagnoses along with the targeted use of diagnostic tests. The referral of unusual cases should be encouraged. In view of the declining autopsy rates in the U.K. it is particularly important that accuracy in clinical diagnosis is pursued.

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ABBREVIATIONS

AD	Alzheimer's disease
AIDS	Acquired Immunodeficiency Syndrome
BSE	Bovine spongiform encephalopathy
CJD	Creutzfeldt-Jakob disease
CVD	Cerebrovascular disease
CSF	Cerebrospinal fluid
EEG	Electroencephalogram
EMG	Electromyelogram
EU	European Union
EUROCJD	European collaborative surveillance group
FFI	Fatal familial insomnia
GSS	Gerstmann-Sträussler-Scheinker disease
hGH	Human growth hormone
gCJD	genetic Creutzfeldt-Jakob disease
iCJD	iatrogenic Creutzfeldt-Jakob Disease
LBD	Lewy Body Disease
MM	Methionine Methionine (genotype at codon 129 of the PRNP gene)
MRI	Magnetic resonance imaging
MV	Methionine Valine (genotype at codon 129 of the PRNP gene)
NCJDSU	National Creutzfeldt-Jakob Disease Surveillance Unit
NEUROCJD	(New) European collaborative surveillance group
PET	Paraffin embedded tissue (blotting)
PRNP	The prion protein gene
PrP^{C}	The normal cellular form of prion protein
PrP^{Sc}	The abnormal, disease-producing form of prion protein (Sc denotes Scrapie)
PSP	Progressive Supranuclear Palsy
PSWC	Periodic sharp wave complexes
sCJD	sporadic Creutzfeldt-Jakob disuse
SSPE	Subacute sclerosing panencephalitis
TSE	Transmissible Spongiform Encephalopathy
UK	United Kingdom
vCJD	variant Creutzfeldt-Jakob disease
VV	Valine Valine (genotype at codon 129 of the PRNP gene)
WHO	World Health Organization

CHAPTER 1: INTRODUCTION

Aims and objectives

The primary aims of this study have been to identify the circumstances in which making a clinical diagnosis of sporadic CJD is potentially problematic within the United Kingdom and to explore ways of improving diagnostic accuracy and enhancing surveillance in these settings.

The main objectives of the study were as follows:

To identify cases of sporadic CJD that were clinically atypical.

To describe in detail the phenotype of atypical cases and assess if particular clinical features are likely to make diagnosis difficult.

To identify cases of sCJD that were not notified to the National CJD Surveillance Unit (NCJDSU) in life and to explore possible reasons for this.

To describe the clinical features and methods of assessing cases of Possible CJD* where the diagnosis remains uncertain. In doing this to discuss ways of improving diagnostic certainty in this group.

To review the alternative diagnoses in pathologically proven non-cases who were suspected of having CJD in life and to examine the clinical features in this group.

To assess the reasons why CJD was suspected in non-cases and to identify factors that may help to distinguish CJD from other diseases.

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* Defined as Possible according to internationally agreed diagnostic criteria. When referring to Possible or Probable cases according to the case definitions in the diagnostic criteria a capital "P" is used.

Transmissible Spongiform Encephalopathies (TSEs)

The infectious agent

Transmissible Spongiform Encephalopathies (TSEs) are a unique group of diseases in that they are thought to be caused by an infectious agent devoid of nucleic acid known as the Prion. TSEs manifest in man either as sporadic, genetic or iatrogenic diseases and are known to be transmissible (as first demonstrated in the chimpanzee in 1968[1]). Although the clinical disease spectrum may (initially at least) be wide, all are characterized by progressive and fatal neurodegeneration. Pathologically there is astrocytic gliosis, spongiform change and varying degrees of cerebral atrophy [2]. The presence of abnormal Prion protein plaques in the brain are considered unequivocally diagnostic [3].

The mysterious nature of the infectious agent has been the focus of much debate. Previous theories speculated that the transmissible, disease-producing agent could be a "slow virus" [4,5] (similar to that seen in subacute sclerosing panencephalitis for example). Against this theory however is the lack of an inflammatory response and the failure to isolate any virus. Also, the agent has demonstrated extreme resistance to processes that would normally cause virus inactivation (e.g. ultra violet and ionizing radiation) leading to the concept (first defined in 1982)[6] of a Prion. A normal cellular membrane prion protein exists (denoted as PrP^C) whose exact function is poorly defined (turning off PrP^C in mice appears to have no overt deleterious effect). There may, however, be a role for PrP^C in resisting oxidative stress via copper/zinc superoxide dismutase[7]. The pathogenic effect of TSEs involves the transformation of this normal, innocent

form of prion protein into the abnormal and destructive PrP^{Sc} (where Sc denotes scrapie). The polypeptide chains of PrP^{C} and PrP^{Sc} are identical in composition but differ in their three-dimensional, folded structures. PrP^{Sc} contains less alpha helix and more beta pleated sheet than PrP^{C}[8]. Once produced the PrP^{Sc} stimulates the conversion of more PrP^{C} to PrP^{Sc}, setting in motion a chain reaction resulting in the accumulation of the disease-producing isoform.

Disease in humans

TSEs are rare. They attract particular focus not only because of their transmissibility and the inherently unusual nature of the infectious agent but also because of the devastating nature of the resulting disease. A heightened interest in this group of diseases has arisen in the United Kingdom following an epidemic of a TSE in cattle in the 1980s (Bovine Spongiform Encephalopathy) and its subsequent likely transmission to the human population in the form of Variant CJD. Other TSEs known to affect humans and animals are detailed in Table 1.1.

Sporadic CJD.

Sporadic CJD (sCJD) is the most common human TSE and exists worldwide (or at least where surveillance systems are in place[9]). Historically, the first reports of a sCJD-like illness were made by two German neurologists in the 1920s (Hans Creutzfeldt[10] and Alfons Jakob[11]) although some of the cases they described would be considered highly unusual for the disease as it is recognized today. sCJD has an incidence of approximately 1 case per 1 million of the population per year (this rises to an incidence of 5 cases per 1 million per year for persons

aged 50-64 years). The peak onset is in the sixth decade [12-14]. A female preponderance has been documented in some studies[15] but not consistently[16;17]. This is postulated to reflect the fact that sCJD is predominantly a disease of older age groups and life expectancy is longer in females (meaning that population demographics may affect the gender distribution). The cause is unknown and there has been no demonstrable link with the animal TSE scrapie or any convincing, repeatable associations with environmental risk factors. It has been hypothesized that the disease is first triggered by a somatic mutation in PrP, leading to the alteration of PrP^{C} by the mutant PrP^{Sc}. The clinical features are of a rapidly progressive dementia with approximately 65% of cases dying within six months[18].

Variant CJD.

Between November 1995 and March 1996 the National CJD Surveillance Unit in the United Kingdom identified ten young people with CJD. These cases raised specific concerns not only because of their age (cases in young people, including teenagers, had been observed before albeit extremely rarely [19-22]) but also because of distinct clinical and neuropathological characteristics. Early psychiatric features were noted to be prominent and some patients complained of striking sensory symptoms. The widespread florid plaques, observed microscopically in the brain tissue of all the cases, were unlike the findings reported in other CJD. The report of these findings, entitled "A new variant of CJD in the UK" was published in 1996 [23].

Considerable evidence exists that vCJD is a consequence of human infection with the BSE agent most probably through ingestion of infected beef. There is a spatial and

temporal association between BSE and vCJD [24;25]. Retrospective studies examining autopsy findings and death certificates have not revealed any cases of previously undiagnosed vCJD[26;27]. The vast majority of vCJD has been observed in the UK and despite enhanced surveillance in other European countries and the United States, Canada and Australia similar patterns of disease have not emerged.

In addition, studies of mice expressing the bovine PrP transgene have revealed the same incubation times, neuropathological features and patterns of PrP^{Sc} deposition regardless of whether the inoculate originated from the brains of BSE cattle or from humans with vCJD[3]. Transmission of BSE to primates results in a similar neuropathological appearance to that seen in humans with vCJD[28;29]. A distinct prion protein structure has been observed in both vCJD and BSE[30;31] and PrP strain typing experiments indicate that vCJD and BSE exhibit the same Prion strain (which differs from that observed in sCJD or scrapie) [32;33].

The range of ages at onset in vCJD is 12-74 years with a median of 26 years[34]. Clinical features in vCJD are relatively distinct and stereotyped with most presenting with psychiatric features and/or a sensory disturbance[35-37]. Common early psychiatric features include dysphoria, withdrawal, anxiety, insomnia and loss of interest [37]. Neurological features may be present at onset and are seen in over 75% by six months [37]. The disease progresses to a dementia with increasing physical debility and a median duration of illness of 14 months (range 6-39 months)[34]

All tested vCJD cases to date have been homozygous for methionine at codon 129 of the prion protein gene[34]. Diagnostically, an abnormal area of high signal observed in

the posterior thalamus on magnetic resonance imaging (the "pulvinar sign") has proved an important, sensitive and non-invasive marker for vCJD[38].

Recent reports indicate that the incidence of vCJD may be in decline[39] although concerns still exist as to the possibility of secondary transmission (for example through blood or blood products)[40] and the possibility of codon 129 heterozygous cases presenting in novel ways.

Genetic CJD.

Genetic CJD (gCJD) is responsible for about 10 to 15 per cent of all CJD [14]. Familial cases of CJD have been reported since 1930 and the transmissibility of gCJD to non-human primates was first reported in 1973 [18]. In gCJD there is an underlying mutation of the PRNP gene leading to the production of a PrP protein molecule thought to be predisposed to developing into PrP^{Sc}. The mutation is inherited in an autosomal dominant manner. Different mutations are associated with different phenotypes and include Gerstmann-Sträussler-Scheinker syndrome (GSS) and Fatal Familial Insomnia (FFI). In some cases the clinical phenotype is similar to sCJD.

Gerstmann-Sträussler-Scheinker syndrome (GSS) typically manifests as a progressive cerebellar ataxia and is associated with mutations at codon 102 (the most common), 212, 217, 117, 198, 145 and 105 of the PRNP gene [14]. Dementia commonly ensues (but is often delayed) and associated features include a spastic paraparesis and extrapyramidal signs[18]. The duration of illness may be much longer than that seen in sCJD, averaging five years [41].

Fatal Familial Insomnia (FFI) was first described in 1986 [42] and subsequently has been described in over 20 families [43]. Sleep disturbance is an early sign (progressing until normal sleep is not possible) along with autonomic dysfunction including increased lacrimation, sweating, raised body temperature and impotence in males [42]. Cognitive impairment usually develops relatively late in the illness [44]. Pathologically there is marked thalamic gliosis with little or no spongiform change [45]. FFI is associated with a mutation at codon 178 of the PRNP gene in the presence of a polymorphism coding for methionine on the affected allele [46]. Onset is usually in the fifth decade with illness durations averaging 13-15 months (range 6-42 months) [47-49]. There are some reports of sCJD with a clinical phenotype similar to that seen in FFI (termed sporadic familial insomnia)[50].

Iatrogenic CJD.

Iatrogenic CJD (iCJD) is the accidental transmission of CJD during medical or surgical treatment. Cases of iCJD have been reported following neurosurgery [51;52]including the use of EEG depth electrodes[53], corneal grafting[54], and human dura mater grafts[55;56]. Iatrogenic CJD has also been reported after the use of cadaveric human growth hormone (hGH) [57] and human pituitary gonadotrophin. The first report of iatrogenic CJD was in 1974 and concerned a recipient of a human cadaveric-derived corneal transplant [54]. This was followed in 1977 by transmission from EEG depth electrodes [53] and the first cases of CJD in human growth hormone recipients were recognized in 1985[58] (over 140 have subsequently occurred). Most of the cases of iatrogenic CJD relate to the use of human cadaveric-derived growth hormone or dura mater grafts [25].

The clinical features in iCJD depend on the route of infection. Peripherally acquired hGH cases (occurring as a result of intramuscular injections of the infected material) generally present with a progressive cerebellar syndrome, often with a delay in the onset of a dementia [59]. Human dura mater cases and those occurring as a result of other neurosurgical procedures, i.e. as a result of direct inoculation into the central nervous system, tend to present with a rapidly progressive dementia similar to that seen in sCJD[12]. In a few of these cases, however, a cerebellar syndrome has been described[60]. There is an association with the incubation period and the route of transmission, with central inoculation leading to a shorter incubation period than peripheral inoculation[14].

Kuru.

Kuru is a TSE, now virtually extinct, confined to the highland regions of Papua New Guinea. The word "kuru" means "to shiver" or "to be afraid" in the local Fore dialect. These symptoms along with cerebellar ataxia are the most striking clinical features of the disease. The first report of a case was made in 1953 [61] and the epidemic reached its peak in 1956 [62]. More than 2600 people have died from the disease since it was first reported [63]. Intensive epidemiological studies concluded that the likely cause of the disease was the practice of ritual cannibalism resulting in the serial passage of an indigenous case of sporadic CJD [14;18] . Women and children were more frequently affected than men and this reflected their practice of eating less desirable body parts (which would include the highly infectious central nervous system). Symptoms were observed in children as young as four years of age.

Table 1.1: Transmissible spongiform encephalopathies of humans and animals

Disease	Host
Creutzfeldt Jakob Disease	
Sporadic	Humans
Variant	Humans
Genetic	Humans
Iatrogenic	Humans
Gerstmann-Sträussler-Scheinker disease	Humans
Fatal Familial Insomnia	Humans
Kuru	Humans (Fore people in Papua New Guinea)
Scrapie	Sheep
Bovine spongiform encephalopathy	Cattle
Transmissible mink encephalopathy	Mink
Chronic wasting disease	Mule, deer, elk
Feline spongiform encephalopathy	Cats
Exotic ungulate encephalopathy	Greater kudu, nyala, oryx

The importance of studying sCJD

Sporadic CJD remains the most common TSE. The significance of previous work into sCJD was highlighted when vCJD was identified. Without previous surveillance work highlighting the clinical phenotype, epidemiological characteristics and pathological features of sCJD it would have been difficult to identify the unusual nature of variant CJD.

As a result of public health concern and interest from the media, attention has tended to focus on vCJD since its emergence in 1996. Sporadic CJD, however, presents several unique opportunities for further study. It is widely acknowledged that the clinical spectrum of disease in sCJD may be diverse[12;13;64;65], sometimes to the extent that even those most experienced in its diagnosis fail to suspect it. This is not the case in vCJD where the symptoms and signs are to date more uniform. The variation in clinical phenotype seen in sCJD makes clinical diagnosis more challenging. For diagnostic accuracy to be maintained a broad understanding of disease manifestations is required. A comprehensive description of the disease phenotype as part of this study will aid pattern recognition and the identification of unusual cases in the future.

Diagnosing all types of CJD accurately is important not only for appropriate counselling, provision of care and monitoring of trends but also because of concerns regarding onward transmission of the infective agent. Contact with potentially infected instruments or tissue without adequate precautions is particulary pertinent in unusual cases of sCJD when the clinical phenotype is not recognised. The study of the phenotypic diversity observed in sCJD may provide further insights into the pathogenesis of prion diseases.

Sporadic CJD differs from vCJD in the genotype expressed at codon 129 of the prion protein gene. In vCJD all clinically evident cases tested to date have been homozygous for methionine (MM) at codon 129. In sCJD, in addition to the MM genotype, valine homozygotes and methionine/valine heterozygotes manifest disease. This genetic variation provides an opportunity to examine the impact of *PRNP* genotype on clinical presentation. This could be useful in aiding the identification of vCJD in non-MM cases in the future.

The emergence of vCJD has shown the importance of seeking a complete understanding of transmission, geographical distribution, risk factors, clinical features and diagnosis even in rare diseases. This study seeks to refocus attention on the clinical features and diagnosis of sCJD in order to add to the understanding of disease manifestations and potential inaccuracies in diagnosis.

Clinical features in sCJD

It should be emphasized that many studies identifying clinical features in sCJD were retrospective and involved examining clinical notes from patients who may or may not have been assessed by a neurologist. This accounts for some variation in the quality of data collected in previous studies and indeed is likely to lead to inaccuracies in reporting. Prospective collection of clinical data by surveillance neurologists is likely to lead to more uniform and accurate documentation of clinical features within a population. This thesis is concerned with clinical data collected largely from clinical examination by a surveillance neurologist, which was collected prospectively using standardized proformas.

Typical sCJD

In order to appreciate the clinical diversity seen in sCJD it is first necessary to define what constitutes a typical case. The typical phenotype of sCJD is one of a rapidly progressive dementia associated with myoclonus and a range of neurological deficits [66]. It has been summarized as:

> Progressive dementia....together with one or more symptoms referable to the pyramidal, extrapyramidal, visual or cerebellar systems. At an advanced stage of illness, myoclonus...and a suggestively abnormal EEG are observed. Death occurs two to five months after the onset of illness as a result of cachexia, intercurrent infection and cardiopulmonary collapse. [67]

When making the diagnosis a triad of classical features may be noted [52;68], consisting of a rapidly progressive dementia accompanied by myoclonus and a characteristic EEG [14]. The mean duration of illness is four months[13] and around 65% of cases have a total illness duration of less than six months [18]. The majority of cases are characterized by a dementia "rapidly leading to a helpless condition and an early death" [64].

Clinical features may vary considerably from individual to individual [12] and oversimplifying the clinical picture may be misleading. Atypical features in sCJD are well recognized as Brown et al concluded in a study of 300 experimentally transmitted cases:

> Sporadic CJD cases show a wide spectrum of clinical features. There are extremes in a continuum of clinical profiles that centre on the more "typical" subacute progression of mental deterioration; cerebellar, visual, pyramidal and extrapyramidal signs; involuntary movements and a periodic EEG. CJD is one disease with a single pathogenesis, expressed in kaleidoscope variety [13].

This study was important as it highlighted phenotypic variations in sCJD. It was however inaccurate in describing CJD as "one disease" when the genetic and iatrogenic forms had already been well-described. Since then, the emergence of vCJD has highlighted that CJD is clearly not a uniform entity and cannot be regarded as a single disease. They may pose problems in identification of cases. An understanding of the breadth of the disease phenotype is important in ensuring accuracy in any surveillance system.

Presenting features in sCJD

The most commonly observed presenting features in sCJD are in order of frequency: dementia, ataxia or visual disturbance [69] (see Table 1.3). A "prodrome" of non-specific symptoms such as weight loss, malaise or personality change has been described by Will and Matthews [64] and noted elsewhere in about one quarter of patients [13]. These prodromal symptoms may be given extra significance in retrospect and it is difficult to be sure of their significance. In one series prodromal symptoms were as common in corresponding hospital controls [12].

Relatively uncommon, but well characterised presentations include the Brownell-Oppenheimer variant [70] which is associated with cerebellar features at onset and the

Heidenhain variant [71;72] (where disease presentation consists of predominantly visual symptoms). An acute presentation, initially mistaken for a stroke, has been described and is thought to occur in up to six per cent [73]This may reflect early inaccuracies in history taking rather than a truly abrupt "stroke-like" onset. Often the progressive nature of symptoms is evident from the outset clinical details are elucidated carefully. Sleep disturbance and a phenotype indistinguishable from Fatal Familial Insomnia has been described sporadically where no mutation in the prion protein gene was found [50]. There are case reports of presentations with cortical deafness [74;75], pruritus [76], progressive and initially isolated aphasia [77;78] a myoclonic alien hand [79] and complex partial status epilepticus [80].

Although the presenting neurological features may be focal, in the majority these are soon engulfed by a rapidly progressive global encephalopathy with an increasing physical dependence, akinetic mutism, dysphagia, periodic respiration and death commonly from bronchopneumonia.

The "Heidenhain variant" of sCJD

The "Heidenhain variant" of sporadic CJD is distinguished from the more typical descriptions of the disease by a profound involvement of visual function at the disease onset. The three original cases were described by a German neurologist, Heidenhain, in 1929[71]. All had pathological changes of a spongiform encephalopathy. In two of the cases there were early, prominent visual symptoms progressing to cortical blindness and both of these were associated with severe pathological change in the occipital lobes of the brain. The third case had early sensory symptoms associated with athetosis of the left upper limb and no associated visual disturbance. In 1954 Meyer et al [72] described the case of a 38 year old man who "became forgetful,

experienced difficulty in concentrating...became irritable, suffered from headaches and his vision began to fail". A right homonymous hemianopia was detected on examination and he died six months after the onset of symptoms. Again pathological changes were most severe in the occipital lobes and they proposed the term "Heidenhain's syndrome".

Visual symptoms are relatively common in sporadic CJD [81] (see Table 1.3) and there is some debate over what constitutes a useful definition of a Heidenhain case. The largest series looking at the incidence and nature of this clinical subtype found that of 169 patients with neuropathologically confirmed sCJD, 34 (20 per cent) met the definition of:

> predominant visual impairments at the onset of disease, consisting of deterioration of vision, blurred vision or visual field restriction, vision loss up to cortical blindness, disturbed perception of colours or structures, optical hallucinations and optical agnosia[82].

Other sources have estimated an incidence of ten per cent if the definition of "presentation with prominent visual disturbance" is applied [81]. These patients would often present first to an ophthalmologist and in recent years have become increasingly recognized within this specialty [81;83].Cognition may be preserved until some weeks into the illness [84] although deterioration is often rapid once a dementia is evident.

Those working in the field of CJD surveillance recognize that a distinct group of patients exist in whom visual symptoms are present in isolation at onset (rather than simply prominent in the context of other symptoms). The above definitions do not distinguish between those who have visual symptoms along with other features at

presentation and those who have visual symptoms in isolation and in this respect the term has been used carelessly. It is the cases who present with isolated visual symptoms that may pose the greatest problems in terms of early, accurate diagnosis and potentially needless eye surgery (for example cataract extraction).

The Brownell-Oppenheimer form of sCJD

About forty years after the original descriptions by Creutzfeldt and Jakob several case reports were published highlighting a fatal ataxia-dementia condition referred to at the time as "an ataxic form of subacute presenile polyencephalopathy (CJD)" [70]. The condition, subsequently named after the two authors of the original report, consisted largely of a rapidly progressive ataxia (preceded by a sensory disturbance in five out of ten patients) followed *some weeks later* by a progressive dementia. It was considered to be a distinct clinical entity with pathological changes similar to those seen in the "larger group of Creutzfeldt Jakob Disease"[70]. Involuntary movements (often myoclonus) were observed in the majority and the mean disease duration in these ten cases was 7.5 months (range two and a half to 13 months). No familial associations were found.

The Brownell-Oppenheimer form of CJD may cause diagnostic uncertainty largely due to the isolated cerebellar features at onset in the absence of an early dementia. A progressive and isolated cerebellar ataxia raises a number of possible diagnoses and CJD is understandably not the foremost. Estimates of the incidence of this virtually isolated cerebellar onset amongst sCJD as a whole are not clearly defined but are likely to be significantly less than one third [13]. Ataxia at onset in sCJD is common but usually occurs with a coexistent rapidly progressive dementia. These circumstances

would not represent a Brownell-Oppenheimer case as it is the virtually isolated cerebellar features at onset that are characteristic of this form of sCJD. The Brownell-Oppenheimer form of sCJD may be particularly distressing because patients maintain insight into their condition for some weeks or months into their illness. Many, however, soon come to resemble the more typical phenotype of sCJD once dementia is present as the rapidity of global decline often mirrors that of sCJD as a whole.

An important differential diagnosis to consider in this group is that of genetic CJD which may also present with a pure cerebellar syndrome [85]. In these circumstances it may be referred to as Gerstmann-Sträussler-Scheinker syndrome (GSS) [86].

Early and dominant cerebellar features, in the absence of familial disease, have been associated with valine homozygosity at 129 of the prion protein gene [87].

Neurological signs in sCJD

Myoclonus is an important clinical sign. During the course of the illness it emerges in approximately 80% of patients [12;13;88] (Table 1.4) although it is rare at presentation. It is most frequently observed in the limbs and usually shows some asymmetry. In sCJD myoclonus is commonly spontaneous but may also be observed in response to sudden noise, touch or light and in these circumstances an excessive startle reaction is also often seen [89]. Myoclonus may be seen in as many as 20% of patients with Alzheimer's disease [90]. It is also recognized in those with dementia with Lewy bodies, leading to some diagnostic confusion [91].

Pyramidal signs are commonly observed (Table 1.4). These tend to consist of hyperreflexia and extensor plantar responses but a definite spastic paresis is unusual. A gegenhalten, paratonic form of rigidity is frequently described and in some studies is considered as a pyramidal sign [64], although often it is regarded separately[88]. Extrapyramidal features, most commonly consisting of lead-pipe rigidity, have been documented with varying frequency in different series (see Table 1.4). This variation is likely to reflect the different classifications of rigidity [64;69;88].

Cerebellar features have been found in between 61% [69] to 86% of patients [92]and usually consist of an ataxic gait, vertigo and nystagmus. Truncal and limb ataxia, tremors and dysarthria occur less frequently [13].

Word-finding difficulties may be an early feature with loss of speech occurring relatively early on in the illness at an average of 13 weeks after symptom onset [93]. Mutism is recorded in up to 100% [64]. Primitive reflexes are present in the majority of cases studied in detail but are not documented in all cases where information was collected retrospectively.

Visual disturbance is frequently encountered and thought to progress to cortical blindness in the majority of cases [12]. Abnormal eye movements have been described in the literature but are uncommon. Most frequently reported is a paresis of conjugate upward gaze (Parinaud's syndrome) seen in five per cent of patients [13]. Individual cranial nerve palsies other than sixth nerve palsies are rarely seen. Documented visual or oculomotor symptoms/signs are listed in Table 1.2.

Table 1.2: Visual symptoms and signs that have been described in sCJD

Blurred vision [13;94]

Diplopia [13;94;95]

Dyschromatopsia [69;84]

Visual distortions (including micropsia and macropsia) [64;82;96]

Visual illusions [97]

Visual agnosia [98;99]

Homonymous hemianopia [97;100]

Visual inattention or neglect [69]

Other visual field loss [101;102]

Palinopsia [103]

Visual hallucinations [68;88;104]

Cortical blindness [71;82;94]

Nystagmus [88]

Supranuclear palsies [13;105;106]

Infranuclear/internuclear palsies [107]

Oscillopsia [95]

Abnormalities of saccades [95;108]

Fundal abnormalities [109;110]

Sensory symptoms may be present in up to 11% [69] and have been described as parasthaesias, itching or pain [16]. Sensory features are generally a more striking feature in vCJD[111].

Seizures are very unusual at presentation and seen in eight [69] to 19% [13] at some stage in the disease. Severe myoclonus may be mistaken for epilepsy and this reflects an intrinsic problem with some of the data used in studies. Reliance is often placed on information gained from the case notes and to an inexperienced clinician myoclonus may be misjudged as representing a seizure. Lower motor neuron signs are relatively rare, reported in approximately ten per cent [69]. Although peripheral nerve involvement has been documented using electrophysiological techniques [112] this was largely sub-clinical and clinically-evident peripheral neuropathies are rare[113]. Many historical "amyotrophic sCJD" cases were, in hindsight, likely to represent motor neuron disease with dementia rather than a TSE. Transmission studies uniformly failed to pass on any infection in these cases[114] calling into question the diagnosis of TSE. A recent review of amyotrophy in prion disease looked at case reports dating from 1968 in pathologically proven (and transmissible) cases. Amyotrophy was defined as *"clinically evident fasciculations with or without electromyographic* evidence of denervation". Clearly this leaves room for error as fasciculations may be regarded as a normal finding in some adults without associated muscle wasting or weakness. Evidence of amyotrophy (according to this definition) was found as an occasionally prominent feature. However, the authors of the study expressed the need for further clarification of both the definition of amyotrophy and its incidence along with neuropathological examination of the spinal cord[115]. Amyotrophic CJD remains a poorly-defined concept.

Patients with an unusual age at onset or long illness duration

Two groups of patients with sCJD stand out from the typical descriptions of the disease because of their young age or long disease duration. These two groups will form part of an overview on atypical cases conducted in this work.

There is a consistently noted association between a relatively young age at onset and a longer disease duration [9;15;65], suggesting overlap between these two groups. Reasons for this may include an increased likelihood of identifying subtle early symptoms in the young and a propensity to artificially feed and therefore sustain young patients. In addition, the inclusion of unidentified familial cases which are associated with a younger age at onset, the absence of other co-morbidity which may hasten death and a slower disease progression per se in the young may influence duration. The longer duration may also reflect different mechanisms of pathogenesis in the young which are not fully understood.

Clinical features of young cases

The mean age of onset of sCJD is about 65 years [12;13;116;117]. The youngest known case of sCJD occurred in a 14 year old [19] but cases under the age of 50 are rare at between three[118] and 12% [13]of total sCJD cases. In those under 50 years of age in France, Germany, Italy, the Netherlands and the UK the incidence rate of sCJD between 1993 and 1995 was calculated at 0.27 per million [119]. The annual incidence in persons aged less than 40 and 30 is approximately 50 and five per billion respectively [9;119].

One of the concerns when the NCJDSU identified the first vCJD cases was that previous diagnoses of sCJD in young people may have actually been vCJD. A review of the pathology in young cases known to the NCJDSU failed to demonstrate that this was the case (Professor James Ironside, personal communication)

Long duration cases

The median duration of illness in sCJD is approximately 4.5 months and approxmately 65% die within six months[18]. Ten to 14 per cent of patients with sCJD live for longer than one year and approximately five per cent live for longer than two years [13;18]. Exceptionally, illness durations of greater than five years have been recorded, although in some of these the question of familial CJD has not been adequately addressed with genetic testing. As the diagnosis in sCJD often rests on the rapid clinical evolution of neurological abnormalities these long duration cases may pose particular problems in reaching an accurate diagnosis in life. Indeed, current internationally agreed diagnostic criteria for sCJD (see Table 1.11) do not allow any case with a disease duration of greater than two years to be classed even as a Possible case*.

It may be impossible to distinguish long duration cases clinically from Alzheimer's disease or other chronic, progressive dementias [120] and the diagnosis may only be recognized upon autopsy. A rare scenario that needs to be borne in mind is that of the coexistence of Alzheimer's disease with CJD, which has been highlighted in several case reports [121-123].

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* Unless an EEG is recorded which shows a typical appearance for sCJD.

Difficulties may exist in deciding whether some symptoms are clinically relevant and erroneously long durations may be noted. For example, amongst those reported with disease durations of greater than ten years some authors have included a slowly progressive anorexia nervosa syndrome [65] and a progressive gait disturbance over 16 years [64] which seem more likely to represent unrelated conditions rather than the onset of CJD.

The largest series of long duration cases [65] identified 33 (nine per cent) of 357 pathologically-proven CJD cases with a duration of two years or more. It is important to note however that 30% of these long duration cases were of genetic CJD. Despite this, an association between younger age at onset illness duration was found which appeared to act independent of genetic factors and has been observed elsewhere[9;15]. Brown et al concluded from this study that the clinical course in long duration cases of sCJD can vary in three ways:

1. An initial, long and slowly progressive first stage of illness followed by a shorter, rapid terminal phase
2. A fairly steadily progressive clinical course with a stepwise addition of increasingly serious neurological abnormalities
3. An initial rapid deterioration followed by a nearly stable or very slowly progressive terminal phase of mute stupor and complete physical dependence.

These observations were echoed in the work of Will and Matthews who summarized the clinical features of cases from 1970-1979 with a duration of illness of greater than 16 months (which they termed an "intermediate form" of CJD)[64]. As genetic analysis was not performed in these cases it is unknown how many had a disease associated

PRNP mutation. The lack of any mutation analysis questions the credibility of thinking of such cases as "sporadic". It is accepted that genetic disease is less likely in the absence of a family history, but by no means excluded.

In Japan the more intensive approach to terminal care in sCJD with advanced supportive measures may partially explain the mean duration of illness of 16.6 months [124]. It does not however account for the observation that the average duration between onset and akinetic mutism was prolonged to 10.5 months, on average, in these cases.

It has been demonstrated that those patients exhibiting periodic sharp wave complexes on the EEG tend to have shortened illness durations when compared with those cases of sCJD without these EEG features [15;125]. This may overlap with the observations linking the genotype at codon 129 of the PrP gene with a characteristic EEG appearance (seen predominantly in methionine homozygotes) and disease duration [87]. By studying long duration cases from the cohort of pathologically proven sCJD cases collected by the surveillance system over a 12 year period this study seeks to test out both the clinical and genetic associations outlined above.

Table 1.3: Presenting features in six clinical studies in sCJD where n>100

(expressed as percentages)

	Brown et al, 1979[67] n=124	Will & Matthews, 1984[64] n= 137	Brown et al, 1986[69] N=230	Brown et al, 1994[13] n=232	De Silva, 1998[88] n=144	Lundberg, 1998[16] n=122
% pathologically confirmed	100[a]	77[a]	100[a]	>95	84	58
Memory loss				48		
Dementia	29	21	31		61	50
Ataxia/cerebellar	29	19	34	33	39	48(inc. vertigo)
Visual disturbance	17	9		19	10	
Oculomotor			6			
Other visual problem			14			
Vertigo/dizziness	8	11	7	13		
Speech disturbance		5 (inc dysgraphia)			4	10 (inc apraxia)
Headache	10	3	7	11		
Sensory	2	4	5	6	3	4
Blackout/seizure		1	<1	0		
Involuntary movements other than myoclonus	1	5	<1	4	1	2

a These studies include between four and ten per cent of familial cases

Table 1.4: Symptoms and signs throughout the course of the illness in six clinical studies of CJD (expressed as percentages)

	Brown et al, 1979 [67] n=124	Will & Matthews, 1984 [64] n=137	Brown et al, 1986 [69] n=230	Brown et al, 1994 [13] n=232	De Silva, 1998 [88] n=144	Lundberg 1998 [16] n=122	Poser et al, 1999 [92] n=201
% PM proven	100[a]	77[a]	100[a]	>95	84	58	51
Dementia	94	100	96			100	96
Memory loss				100	64		
Disorientation					78		
Ataxia		62				80	86
Cerebellar signs	56	42	61	71			
Incoordination					85		
Nystagmus					20		
Myoclonus	84	82	88	78	85	75	89
Other mvt disorder	32		26	36		53	
Chorea					13		
dystonia					16		
Visual	40		42	42			
Disturbance		33				18	54
Hallucinations		17	16		32	25	
Blindness		13			52		
Oculomotor					27	28	
Pyramidal signs	44	79 (inc rigidity)	43	62	62		52
Extrapyramidal	60	3	67	56			73
Muscle rigidity					38		
Parkinsonism					34		
Sensory disturbance	7			11		16	
Seizures	9	9	8	19	13	28	12

[a] These studies include between four and ten per cent familial cases

The role of diagnostic tests in sCJD

Although neuropathological examination of brain tissue remains the "gold standard" for diagnosis in CJD, recent advances in the utilization of specific diagnostic tests have greatly enhanced clinical diagnostic certainty. Less is known, however, about the value of these tests in specific clinical contexts (e.g. with clinically unusual cases). The degree to which investigations are employed by the clinicians directly involved with patient care is also uncertain. This study will examine these issues.

Cerebral magnetic resonance imaging

Several features on cerebral MRI have been recognized in sCJD but they are not considered specific enough to be included in the internationally recognized diagnostic criteria (Table 1.11). The MRI scan may be normal in sCJD[105;126]. Abnormalities described include atrophy, basal ganglia and thalamic changes and cortical hyperintensity.

Atrophy on MRI in sCJD.

Brain atrophy is a non-specific finding and therefore not useful in differentiating sCJD from other neurodegenerative diseases. It has been described in about 30% of cases in two separate studies[126;127]. Patterns of atrophy may be focal or generalized[128] and as the disease progresses the development of increasingly severe atrophy has been observed [127;129]. Generally the presence of cortical atrophy is a late feature and correlates with the duration of disease [105;129].

High signal in the basal ganglia in sCJD.

The first series that identified abnormal areas of high signal in the caudate head and putamen on MRI found 79% of 29 patients displayed these abnormalities on T2 and proton density sequences [105]. A larger German study observed basal ganglia high signal changes in 67% [127]. These basal ganglia changes can be difficult to interpret in people below the age of 40 years because of intrinsic intermediate signal intensity of the putamen and globus pallidus seen in normal individuals [130]. Basal ganglia changes have been observed as early as three weeks after onset of symptoms [131] and have been recorded before typical EEG changes were evident [132]. Less frequently hyperintensity is observed in the globus pallidus, thalamus and periaqueductal grey matter [127].

One of the difficulties with the MR abnormalities in the caudate head and putamen are the fact that they can also be seen in other diseases. Similar appearances have been described in hypoxic encephalopathy, carbon monoxide poisoning, hypoglycaemia, haemolytic uraemic syndrome, encephalitis, mitochondrial disorder's (e.g. Leigh's disease), Wilson's disease and Huntington's disease [133;134]. However, it is usually possible to differentiate between these disorders and sCJD clinically and specificity for sCJD may be as high as 93% amongst those thought clinically to have sCJD[105].

Cortical hyperintensity in sCJD.

Cortical high signal is reported less frequently than the changes observed in the basal ganglia. The best estimate of prevalence comes from the series of 29 patients mentioned above, where 14% displayed signal change in the cortex [105]. High signal in

the cortex has been reported soon after disease onset (before high signal in the basal ganglia was observed) and may therefore be regarded as a relatively early sign [98;135-137]. Ribbon-like hyperintensities in the cerebral cortex have emerged as a potential aid to diagnosis early in the condition when diffusion weighted imaging is employed [138]. These abnormalities may be present when both the EEG and CSF are not diagnostic [139-141].

The Electroencephalogram (EEG)

The characteristic EEG pattern seen in sCJD is that of periodic, sharp wave complexes (PSWCs) seen throughout the recording [12;142;143] as shown in Figure 1.1. Studies report a prevalence of this abnormality of between 55 per cent and 85 per cent [13;64;144] of patients with sCJD. This figure is likely to be in decline, however, as serial EEG recordings may no longer be frequently employed since the advent of other diagnostic tests (such as CSF 14-3-3). A large, prospective, multi-centre study of 219 sCJD cases found a "typical" EEG had a sensitivity of 66% and a sensitivity of 74% [145]. One of the difficulties with all of the studies looking at the prevalence of a typical EEG appearance is absence of or discordance in the definition of a "typical" recording. Within the UK surveillance system a five-level EEG grading system is employed (Appendix 2) and each EEG is reviewed by one of two NCJDSU doctors blinded to the diagnosis. In many other centres reporting from local physicians is not reviewed separately and it is unclear if EEG grading is standardised, potentially leading to bias in any estimates of the prevalence of typical EEG recordings.

The appearance of PSWCs depends on the clinical stage of the illness, being more often seen later in the disease [142;146;147]. A typical recording is more commonly seen in those with a MM1 genotype at codon 129 of the PRNP gene [87]. From a clinical

perspective it has been shown that a duration of illness of greater than one year or a presentation with ataxia make the development of PSWCs less likely [65;69]. The EEG appearance is considered specific enough to be included in the internationally agreed diagnostic criteria (Table 1.11). Other causes of a "sCJD-like" EEG may cause confusion (Table 1.5) if not excluded.

Table 1.5: Causes of a "sCJD-like" EEG*

Alzheimer's disease[92]
Hepatic encephalopathy[148;149]
Hypoglycaemia[150]
Post-anoxic encephalopathy (NCJDSU archive, [151;152]
MELAS[153]
AIDS dementia[154]
Hyperparathyroidism[155]
Lithium toxicity[156]
Mianserin[157]

* Other condition reported to cause a similar picture but either reported to be "suggestive" only or not reproduced include normal pressure hydrocephalus, cerebral lipidosis, holoprosencephaly, lymphoma, hyperammonaemia, multiple myeloma, hypo and hypernatraemia, cerebral abscesses, amitriptylline toxicity, metrizamide toxicity and Lewy body disease. (List reproduced from "A new variant of Creutzfeldt-Jakob disease in the United Kingdom" MD thesis by Martin Zeidler, with the written permission of the author).

Figure 1.1: A "positive" EEG in sCJD

CSF 14-3-3

14-3-3 is an abundant, acidic brain protein which, when detected in the cerebrospinal fluid of individuals with a clinical picture consistent with CJD, has significant diagnostic value[158-160]. The reported sensitivity of 14-3-3 ranges from 77 to 100 per cent [159;161;162] with specificities of between 87 and 100 per cent [159;161]. Central to the accuracy of the test is the selection of the patient group because false positive results are well documented in other conditions. These, however, are often clinically distinct

from sCJD [162-165]. Table 1.6 lists some of the other diagnoses found in cases referred to the NCJDSU for CSF analysis only.

CSF 14-3-3 was recently incorporated as a diagnostic test in World Health Organisation (WHO) and European Union (EU) criteria for sCJD[166;167] (see Table 1.1). This decision followed a large, multi-centre prospective study that found a positive predictive value of 94% and a negative predictive value of 82% amongst clinically Possible cases [145].

Table 1.6: Diagnoses in patients with positive CSF 14-3-3 referred to the NCJDSU in 2003 for CSF analysis only

34

Diagnosis (number of patients)
Unspecified psychiatric disorder (2)
Improved (1)
Demyelination (1)
Hyponatraemia and seizures (1)
Neuropathological examination not consistent with CJD (1)
Neuropathologically proven encephalitis (1)
Lewy Body Disease (1)
Hydrocephalus (1)
Vascular Disease (1)
Motor neurone disease (1)
Probable CNS inflammatory disorder (1)
Unspecific encephalopathy (1)

The Differential diagnosis of sCJD

Approximately one half of patients referred to the NCJDSU have a final diagnosis other than CJD or the diagnosis remains uncertain. Differentiating between CJD and other neurodegenerative diseases accurately has implications for the patient, the family, health care providers and potentially the wider community. Although in many cases distinguishing clinically between sCJD and other diseases may not be problematic, this study seeks to identify the cases that are difficult to diagnose clinically and what features make diagnosis problematic. Table 1.7 outlines the most common differential diagnoses of CJD found in three surveys.

Other neurodegenerative disorders and sCJD

Previous studies have demonstrated that the most common diagnosis in postmortem confirmed non-cases is Alzheimer's disease[64;92].There may be particular difficulty distinguishing between sCJD and Alzheimer's disease with myoclonus, especially when the Alzheimer's disease is of short duration[92]. To add to the diagnostic confusion the typical EEG of sCJD has been described in Alzheimer's disease [92;168].

One study compared the clinical features of 31 cases of pathologically-proven Alzheimer's disease and Lewy body dementia (who in life were considered to have sCJD) with a control group of 25 patients with sCJD. They found that dementia, rigidity and myoclonus were common in all three groups and recommended that, when faced with this triad, CJD should be the first line diagnosis but that Alzheimer's disease should be considered if the disease course is longer and Lewy body dementia if parkinsonism or fluctuations in clinical state were present[91].

Although broadly useful, this work did not identify clear differences that could be applicable in individual cases. This reflects the overlap between the disorders sometimes seen. More should be done to encourage autopsy in unusual cases.

Genetic, iatrogenic and variant CJD as differential diagnoses of sCJD

The other main differential diagnoses of sCJD are other types of CJD. Genetic CJD (gCJD) may present in a similar fashion, particularly when the disease is associated with the E200k mutation in the prion protein gene [169] and genetic testing should be offered routinely, even in the absence of a family history of CJD. The diagnosis of probable iatrogenic CJD (iCJD) rests on the identification of exposure to the infective agent coupled with clinical evidence of a TSE. In some cases the possibility of sCJD cannot be excluded. The presence of prominent and early cerebellar features may alert a clinician to iCJD as a potential diagnosis. Sporadic CJD can present in this manner, however, as the previously described Brownell Oppenheimer form.

Some cases of sCJD may present with features more commonly associated with vCJD. In 30 cases where vCJD was originally suspected sCJD was the diagnosis proved at autopsy in nine[170]. The distinction between variant and sporadic CJD may become more difficult in atypical longer duration cases or when the patient is young. A recent case report of a 36 year old woman with sCJD who presented with psychiatric features highlighted these difficulties[171].

Case reports exist of a range of other conditions mistaken for sCJD. These are summarised in Table 1.7 and Table 1.8.

Table 1.7: The differential diagnosis of sCJD in three studies*

(numbers in brackets indicate cases with neuropathological data)

Diagnosis	England and Wales 1970-79[a](n=42)[12]	England and Wales 1980-1994[b] (n=95)[12]	Germany 1993-1996[c] (n=124)[92]
Alzheimer's disease	20 (3)	28 (5)	34 (13)
Cerebrovascular disease	2 (1)	4	11 (3)
Unclassified dementia	-	-	20 (1)
Chronic encephalitis of unknown cause/idiopathic encephalopathy	2 (2)	45 (5)	10 (4)
Motor neuron disease	5 (1)	1 (1)	3 (2)
Parkinson's disease	1 (2)	1	6
Psychiatric disease	-	1 (catatonic schizophrenia)	6
Paraneoplastic syndromes	1	1	3
Hydrocephalus	-	1 (3)	-
Multiple sclerosis	1	1 ("atypical demyelination")	3 (1)
Pick's disease	1 (1)	1 (1)	-
Hashimoto's encephalitis	-	-	2
Corticostriatonigral degeneration	3 (3)	-	2

Other diagnoses found at autopsy include the following (found in single patients only): leucodystrophy, fatal familial insomnia, congophilic angiopathy, lipoid histiocytosis, alcohol induced atrophy, gliomatosis cerebri, hypoxic brain damage, astrocytoma.

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[a] Cases certified as dying of CJD in which the diagnosis was reclassified after review of clinical data or pathology

[b] Cases referred as suspect CJD in which the diagnosis was reclassified after review of clinical data or pathology

[c] Cases referred as suspect CJD with neuropathologic confirmation of alternative diagnosis

Other diagnoses (where findings at autopsy are not specified) each for n=1 in England and Wales studies: Herpes simplex encephalitis, familial spinocerebellar degeneration, multiple cerebral abscesses, stroke, carcinomatous meningitis, glioblastoma, post-anoxic encephalopathy, cerebral metastases, hepatic encephalopathy, progressive supranuclear palsy.

Table 1.8 Additional reports of conditions mistaken for CJD

(Based on information presented in an MD thesis by Martin Zeidler[25] and used with written permission of the author)

Diagnosis	Reference
Neoplastic	
Reticulosarcoma	Brown et al, 1986[69]
Angiotrophic lymphoma	Drlicek et al, 1991[172]
Infective	
Cryptococcal meningoencephalitis	Gadea & Soriano, 1999[173]
Subacute sclerosing panencephalitis	Brown et al, 1994[13]
AIDS dementia	Thomas & Borg, 1994[154]
Metabolic	
Hypoglycaemia	Kida et al, 1988[150]
Hyperparathyroidism	Bertolucci & Malheiros, 1990[155]
Mitochondrial encephalopathy	Isozumi et al, 1994[153]
Drug-induced encephalopathies	
Bismuth	Von Bose & Zaudgig, 1991[174]; Gordon et al, 1995[175]
Amitriptylline	Foerstl et al, 1989[176]
Mianserin	Koponen et al, 1990[177]
Lithium	Broussolle et al, 1989[178]; Casanova et al, 1996[179]; Finelli, 1992[180]; Kikyo & Furukawa, 1999[156]; Masmoudi et al, 1996[181]; Primavera et al, 1989[182]; Smith & Kocen[183], 1988;
Baclofen	Lazzarino et al, 1991[184]
Miscellaneous	
Extradural haematoma	Brown et al, 1994[13]
Sarcoidosis	Brown et al, 1994[13]
Bilateral internal capsule haematomas	Brown et al, 1994[13]
Neuroaxonal dystrophy	Brown et al, 1986[69]
Bilateral Ammon's horn atrophy	Brown et al, 1986[69]
Ceroid lipofuscinosis	Brown et al, 1994[13]

Disease surveillance

All of the data used in this study have been collected through a disease surveillance system. An understanding of how this system has evolved along with an appreciation of the basic principles of disease surveillance is essential to appraise the quality and content of the data. Disease surveillance may be defined as:

> "Ongoing scrutiny by methods that are practical, uniform and rapid. It has the purpose of detecting changes in trends or distributions, in order to initiate investigations or control measures" [185]

To be effective, a surveillance programme should involve the dissemination of aggregated data so that disease control and prevention can be enhanced [186]. A good surveillance system is required to be simple, flexible, acceptable, timely, sensitive to detecting episodes of a condition, have a high positive predictive value, be representative of the disease in a population and ideally to be cost effective [187]. Data collected from disease surveillance is useful for monitoring trends, identifying emerging epidemics and describing and classifying new clinical syndromes. It allows effective planning and implementing of control measures as well as allocation of health resources appropriately. Surveillance can direct research and provides an excellent base for policy decisions. Ongoing data collection helps to assess the success or failure of control programmes.

CJD surveillance in the United Kingdom

A historical perspective.

CJD surveillance in the United Kingdom began in England and Wales in 1979 with a retrospective study attempting to identify all cases of CJD that occurred during the previous nine years [188]. The 152 cases identified in this study were ascertained from three sources: death certificates, a previous study of pathologically-proven cases and by direct notification from neurologists and neuropathologists. It is very likely that underascertainment was significant during this period as there was no prospective surveillance programme in place. It did, however, provide a starting point for CJD surveillance in the UK. Most surveillance systems rely heavily on reports from health care providers of suspected cases. Completeness of such "passive" reporting varies considerably depending on the characteristics of the disease in question [189], the severity of the disease and its perceived public health importance [190]. Underreporting may be exacerbated by a lack of knowledge of which diseases should be reported, not knowing how to report appropriately, concerns about confidentiality and a perception that the list of diseases to be reported is too extensive [191]. The relatively low profile of CJD at this time may have contributed to the lower incidence of the disease observed during this period.

Criteria for the diagnosis of CJD (see Tables 1.9 and 1.10) were employed and cases were classified as Definite, Probable or Possible on the basis of available clinical and pathological information. The development of a standardized case definition is important for any disease under scrutiny for diagnostic accuracy and to allow comparison of data between centres. A case definition needs to be simple, acceptable, understandable and have diagnostic criteria that are unambiguous [192]. Since the

inception of CJD surveillance within the UK the diagnostic criteria have undergone several amendments (see Table 1.9, 1.10 and 1.11) and these are discussed below.

The average annual incidence of CJD (which included sporadic and familial forms) from the 1970-1979 retrospective study was 0.32 cases/million, with a peak mortality rate in the 65-69 year age group. Clearly this figure is inaccurate as case ascertainment during that period was limited. In 1980-1984 prospective surveillance for CJD in England and Wales was initiated and an average annual mortality rate (similar to incidence rates owing to the mean duration of illness of approximately four months) of 0.49/million was detected [193]. Patients were seen in life whenever possible by a surveillance neurologist following voluntary referral from a clinician with identification from death certificate notification and autopsy continuing. From 1970-1984 a total of 267 patients with definite or probable CJD were detected. There was no space-time clustering of date and geographical location of onset. A case control study undertaken with 72 of the cases and 144 age and sex-matched controls did not find any evidence that cases had lived closer to each other than controls, except that more cases had lived in London [193]. Cases occurring between 1985 and 1990 in the UK were identified retrospectively.

The National CJD Surveillance Unit (NCJDSU) was established in Edinburgh in 1990 in response to the emergence of the epidemic of BSE in the late 1980s and upon the recommendation of the Southwood report [194]. The primary aim of the NCJDSU was to identify any change in the characteristics of CJD within the UK that might be linked to the emergence of BSE. The previous surveillance data from the 1970s and 1980s were invaluable in providing a reference point for clinical and epidemiological characteristics of CJD within the UK. The basis for re-establishing prospective CJD surveillance rested on the premise that if BSE infected humans it would be most

likely to cause disease manifestations similar to those already observed in CJD and that some or all of the following phenomena might be observed[195]:

An increase in the overall incidence of CJD within the UK
An excess of cases in groups most likely to have high exposure to the causative agent of BSE
A change in the epidemiological pattern of CJD, such as a change in the age distribution
A change in the clinical or neuropathological characteristics of CJD

Case notification and data collection.

Since 1990, referral of suspect cases to the NCJDSU has continued in three ways:
Clinical passive ascertainment from neurologists, neuropathologists and neurophysiologists. These groups of doctors are reminded annually of the need to refer any individual with a possible diagnosis of CJD[a].
Death certificates[b]. Passive ascertainment occurs with cooperation from the Office of National Statistics for England and Wales and the General Register Offices for Scotland and Northern Ireland. All death certificates coded under the rubrics 046.1(Jakob-Creutzfeldt disease subacute spongiform encephalopathy) and 331.9

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[a] The underlying assumption from the targeting of certain professionals with reminders to refer is that the clinical presentation of CJD will result in referral for a medical opinion and, ultimately, referral to a neurologist [196]. This assumption is borne out by work conducted in the UK and France [66].

[b] The proportion of cases of sporadic CJD ascertained by death certificate has fallen from 13% in 1980-84 to 6% in 1990-92. For the years 2000 to 2001 only 2 cases of sporadic CJD were identified in this way. No case of vCJD to date has been identified solely by death certificate.

(other cerebral degenerations, unspecified) according to the 9th International Classification of Disease revision are supplied to the NCJDSU.
Other sources. Passive ascertainment also occurs from psychiatrists, paediatricians, geriatricians other health professionals and relatives.

CJD within the UK has not been made a notifiable disease as previous experience has shown that statutory referral may not be the best way of detecting cases especially if referral of unusual phenotypes is desired [25]. A key aim of the surveillance unit is to identify atypical cases [196]. Due to the fact that the primary aim of the unit was to identify cases of CJD that may have occurred as a result of BSE exposure, cases of familial and iatrogenic CJD are not assessed in detail.

Case definitions.

The case definitions for both sporadic and variant CJD have undergone several revisions since the NCJDSU was founded. The initial case definition for suspected CJD was adapted from that developed by Masters et al in 1979 [117](see Table 1.9). This relied on the presence of certain clinical features along with neuropathological confirmation. In 1993 at the second meeting of the European Collaborative Study Group on CJD, the criteria for sCJD were slightly modified (NCJDSU minutes of Rome surveillance meeting, unpublished) (see Table 1.10). The most recent amendment to the sCJD criteria currently used in the UK and Europe took place in 1998 (NCJDSU minutes of Rotterdam surveillance meeting, unpublished) (see Table 1.11). It followed an analysis of the sensitivity and specificity of CSF 14-3-3 as a diagnostic test and its subsequent validation [145]. Analysis of the final diagnosis of those classed as Probable sCJD who subsequently had a postmortem examination revealed that the current diagnostic criteria for Probable sCJD have a positive

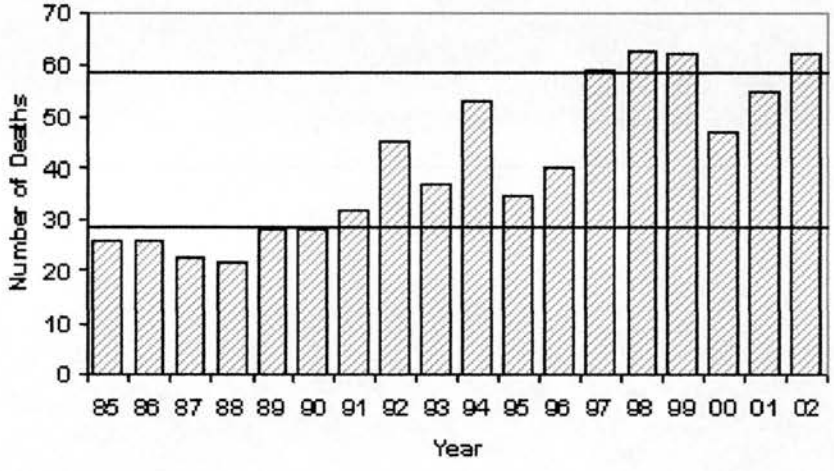
predictive value of 97% [145]. Autopsy confirmation of CJD remains the gold-standard in diagnosis.

The case definition currently in operation for vCJD was devised by a WHO working group in Edinburgh in 2001 and is detailed in Appendix 1. To date all cases with a diagnosis of Probable vCJD who have subsequently had postmortem examinations have been confirmed cases.

The incidence of sCJD in the UK

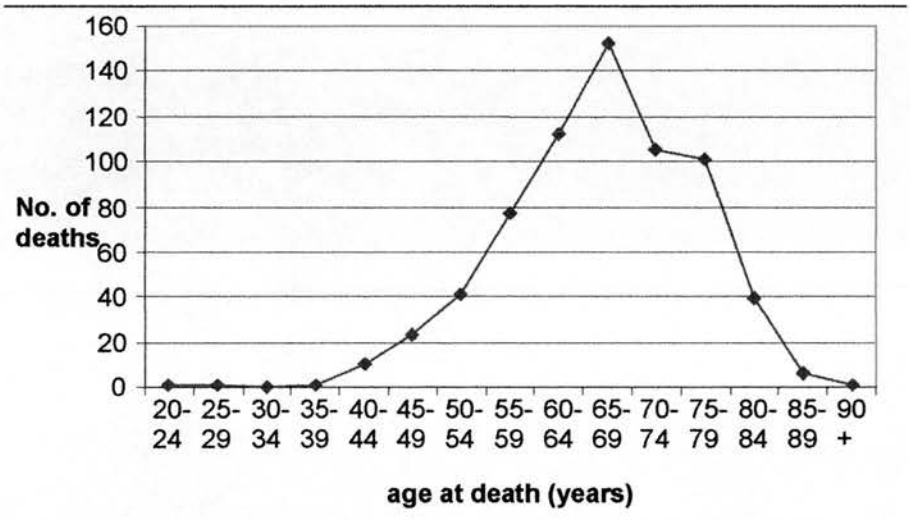
An increase in the number of cases of sCJD has been observed in the UK since the 1970s. During the period of prospective surveillance in 1980-84 the yearly number of deaths from sCJD in the United Kingdom averaged 24.8. During prospective surveillance implemented after the onset of the BSE epidemic (1990-1996) the yearly number of deaths averaged 33.6. From 1996-2002 the number of deaths rose to a yearly average of 56 (NCJDSU data) as illustrated in Figure 1.2.

Figure 1.2: Number of deaths per year from sCJD in the United Kingdom, 1985-2002[34]



These increases are largely thought to be due to improved case ascertainment and had been anticipated [197] as methods of surveillance improved. The earlier work was not likely to have been accurate in terms of calculating incidence. The increased case numbers have predominantly been witnessed in the older age groups: case numbers in patients over 70 years of age more than doubled from the period 1980-85 to 1990-95 [195]. A similar increase in numbers of sCJD has been observed in Europe, also showing the differentially enhanced ascertainment in the older age group [118;119]. Concerns remain however that cases of both vCJD and sCJD in the elderly may be being missed. Previous reports estimate that only about four per cent of elderly patients dying with dementia have an autopsy [198]. Concerns have been raised over the impact of decreasing postmortem rates on the potential detection of CJD cases [199]. Figure 1.3 illustrates the number of deaths from sCJD from 1990-2003 according to the age of the patient and demonstrates a decreasing number of cases after the age of 69.

Figure 1.3: Number of deaths from sCJD 1st May 1990-31st October 2003 according to age group



CJD Surveillance in Europe and other allied countries

The European Union (EU) prospective collaborative study of CJD was initiated in 1993. This occurred largely as a result of the BSE epidemic and for the same reasons that the NCJDSU was established in the UK. By the year 2000 Belgium, France, Ireland, Netherlands, Portugal, and Switzerland had all reported cases of BSE in their cattle albeit at much lower levels than in the UK. The collaborative study has the additional aim of harmonizing research methods of national surveillance across international borders and now includes some countries outside Europe*. In addition to a further development of the case definition for CJD [145] this work has led to comparative incidence studies [200-202] and analyses of risk factors through case control studies [203-206].

* Australia, Austria, Belgium, Canada, Finland, France, Germany, Greece, Iceland, Israel, Italy, the Netherlands, Norway, Portugal, Slovakia, Spain, Sweden, Switzerland, UK, USA are all involved in this programme.

Table 1.9 Case definition of CJD according to Masters et al, 1979[117]

Definite CJD

Neuropathologically-confirmed spongiform encephalopathy in a case of progressive dementia with a least one of the following features:

1. Myoclonus
2. Pyramidal signs
3. Characteristic electroencephalogram
4. Cerebellar signs
5. Extrapyramidal signs

Probable CJD

Neuropathologically unconfirmed cases with the same clinical features described above

Possible CJD

History (without medical records allowing confirmation) of progressive dementia with:

A. Myoclonus and a course of less than three years; or

B. A member of the family having transmissible definite or probable CJD; or

C. At least two of the clinical features listed for definite CJD together with the appearance of prominent and early signs of lower motor neuron involvement (the amyotrophic form of CJD).

Table 1.10 Case definition for sCJD as revised by EUROCJD in Rome, 1993

Definite
Neuropathologically-confirmed
Probable
Progressive dementia
Typical EEG
At least two out of four of the following clinical features:
Myoclonus
Visual or cerebellar features
Pyramidal/extrapyramidal features
Akinetic mutism
Possible
Three out of four of the clinical features listed above
No EEG or an atypical EEG
Duration less than 2 years

Table 1.11: Current Case definition for sCJD in the UK and Europe

I	Rapidly progressive dementia	
II	a	Myoclonus
	b	Visual or cerebellar features
	c	Pyramidal or extrapyramidal features
	d	Akinetic mutism
III	Typical EEG	
Definite:	Neuropathologically/immunocytochemically confirmed	
Probable:	I + 2 of II + III	
	or	
	Possible + positive 14-3-3	
Possible:	I + 2 of II + duration < 2 years	

CHAPTER 2: METHODOLOGY

The study sample

All patients included in this study had pathologically-proven sCJD and were known to the NCDJSU. Patients were included who had been referred between January 1990 and the end of December 2002. Those cases referred at the end of 2002 but in whom autopsy results were pending at the time of data collection were not included. Any cases of suspect sCJD without neuropathological confirmation were excluded. The total number of cases included in the study was 485. Cases were exluded if PRNP mutation analysis revealed a mutation. Not all cases had complete mutation analysis. Exact numbers of cases with full PRNP gene analysis are outlined in the results section.

Cases referred to the NCJDSU with suspected CJD

Individuals with suspected CJD are referred to the NCJDSU either by passive ascertainment from clinicians, death certificates (provided by the Office of National Statistics) or from neuropathologists after a post-mortem examination revealed CJD. Occasionally relatives or a member of the general public refer a suspect case. Enquiries and referrals are dealt with initially over the telephone by a NCJDSU doctor. Increasingly patients are referred initially for CSF 14-3-3 analysis but these are not classified as "referrals" automatically (this depends on the clinical details of the request).

When a referral of a suspect case is made a unique identification number is assigned to that individual patient. If the patient is referred before death an assessment is

made of the likelihood of CJD based on the clinical features and investigation results. The patient is classified according to the case definitions for sCJD (see Table 1.11) or vCJD (see Appendix 1) as a Definite, Probable, Possible or a likely "non-case". In this study these classifications are denoted by a capital letter to differentiate them from, for example, the *possibility* that the diagnosis may be CJD.

The definition of clinical subgroups

The following headings describe the patient groups that formed the basis of this study:

Cases defined as "atypical" sCJD

Cases of sCJD only notified to the NCJDSU after autopsy

Cases classified as Possible sCJD who had not gone on to have an autopsy

Pathologically-proven Non CJD cases where CJD had been suspected in life

Defining "Atypical" sCJD

For the purposes of this study, cases that are defined here as Atypical shall, from now on, be denoted with a capital letter "A". This is done in order to indicate that the word refers to a strictly defined group of cases rather than an adjective that may be used based on undefined criteria. In order to define Atypical sCJD it is important to understand what constitutes a typical case. Features of a case of sCJD that are generally considered typical include:

A short duration of illness (of less than six months)

An age of onset at around 65 years

The presence of supportive investigations (namely periodic sharp wave complexes on an EEG and a positive CSF 14-3-3)
An MM genotype
A presentation with dementia and the subsequent rapid evolution of symptoms
A Probable diagnosis when the clinical diagnostic criteria are applied

The aim of defining "Atypical" was to identify those cases of sCJD exhibiting features that were unlike those typically associated with the disease. The features considered in this process are as follows:

A long duration of illness.

One of the most striking features of sCJD is the rapidity of the physical and mental decline that is often observed. Sporadic CJD cases with a longer illness duration may lack this characteristic rapid deterioration. When patients with sCJD live for longer than two years other neurodegenerative conditions (such as Alzheimer's disease) may be considered far more likely. Cases with a disease duration of greater than two years are of particular interest in this study because they all fall outside of the case definition for sCJD (which stipulates a disease duration of less than two years unless the EEG is typical).

A young age at onset.

Young cases are unusual in sCJD and for this reason the diagnosis may not be suspected initially. A young age at onset may lead to confusion with vCJD. Studying these cases is important in understanding if the phenotype of sCJD is different in the young and reasons why variability in phenotype may occur. Disease onset below the

age of 50 years occurs in only about five per cent of cases: a sufficiently small proportion for these cases to be regarded as Atypical.

The PRNP codon 129 genotype.

An association between a MV or VV genotype and unusual clinical features has been described although authors have disagreed as to the extent of this correlation [87;207]. About 35% of patients with sCJD possess a MV or VV genotype at codon 129. If all these were taken to be Atypical on this basis alone then a large number of cases would be involved. An alternative way of examining any association between phenotype and genotype is to identify cases by unusual clinical features alone (i.e. blinded to genotype) and then retrospectively examine the genotype results. This method would eliminate selection bias in determining whether or not the hypothesis was correct and was the method used in this study. Therefore codon 129 genotype was excluded from the definition of an Atypical case employed in this study.

Investigaton results: the EEG, CSF 14-3-3 and cerebral MRI.

A review of the results of EEG recordings undertaken on pathologically-proven sCJD was performed in order to identify the proportion of positive and negative tracings. It was found that only 39% of cases between 1990 and 2002 (who had had an EEG recording performed) had exhibited a positive tracing. If a negative EEG was to be included in any definition of Atypical it would result in the majority of cases (61%) being considered Atypical on this basis alone.

CSF 14-3-3 has a sensitivity of 94% in cases with pathologically-proven sCJD referred to the NCJDSU for CSF analysis[34] and therefore a negative result is regarded as

unusual. If CSF 14-3-3 was negative but all other clinical features were typical it would be unlikely, in practice, to consider a case unusual on that basis alone. As there are sometimes technical difficulties with the storage or transport of CSF specimens a negative result in the context of an otherwise typical case may raise doubts regarding the accuracy of the result. If unusual cases are identified on clinical grounds alone and investigation results are examined subsequently then an assessment of the role of the test in differing clinical scenarios can be made. For the purposes of this study this approach is considered a better way of examining the role of CSF 14-3-3 in Atypical cases.

It is not known whether or not basal ganglia high signal on cerebral MR correlates with specific clinical features. This is assessed as part of this study but MRI findings are not included in any definition of Atypical.

Unusual features at presentation and the delay in the onset of cognitive decline.

Typically sCJD presents with symptoms of a cognitive decline (e.g. memory loss, confusion or disorientation). Other focal symptoms occasionally occur at onset where impaired cognition is not a prominent early component. Visual symptoms in isolation at onset are well recognised (the Heidenhain variant of sCJD) as are predominant or virtually isolated cerebellar features (Brownell-Oppenheimer form). Other focal onsets may cause diagnostic problems if cognitive decline is delayed, for example the presentation with an isolated involuntary movement or a pure psychiatric symptom. Assessing whether cognitive decline is delayed is largely dependent on the clinical history from any family and documentation by involved clinicians. Many patients would not undergo detailed neuropsychological testing and therefore the judgement as to whether a

cognitive decline is present or absent is largely a clinical one. Psychiatric symptoms alone, for example, may not be perceived as representing a cognitive decline, as is often the case in vCJD. Cases exist that are not typical for sCJD because of the perceived absence of any cognitive decline (usually early in the illness).

By defining unusual clinical presentations (such as pure visual, pure cerebellar or cases where an apparent cognitive decline is delayed) it is possible to assess the amount of diagnostic difficulty caused. It also enables an assessment of whether disease presentation is a marker for an unusual disease progression.

Cases not given a Probable or Possible diagnosis according to the current clinical diagnostic criteria.

Any group that does not meet the clinical diagnostic criteria for sCJD is likely to include a number of clinically unusual cases. The problem of incomplete data, due to a lack of available medical information, prevents any analysis of this group being meaningful. If a patient is referred but clinical data are sparse they often do not meet the criteria for a Possible case. Some patients are not examined neurologically whilst unwell and in other instances access to medical notes may be denied or problematic. This category would be likely to include a significant number of patients with poor clinical information who may or may not be clinically Atypical.

A summary of the definition of an Atypical case used in this study

An Atypical case of sCJD was defined in this study according to the following characteristics:

A duration of illness of two years or more

An age at onset of less than 50 years

Presentation with pure visual symptoms in isolation for at least two weeks

Presentation with a cerebellar syndrome and no evidence of a cognitive decline* for at least one month into the illness

Presentation with another focal symptom (i.e. not visual or cerebellar) and no evidence of a cognitive decline* for at least one month into the illness

A comparison group: "Core sCJD"

In order to make comparisons regarding Atypical cases a group of pathologically proven sCJD cases who were not Atypical were identified. They are referred to here as "Core sCJD". The defining characteristics of this group were the presence of all of the following:

Age at onset 50 years or more

Duration of illness less than two years

Documented evidence of a cognitive decline within the first month of the illness

Not presenting with visual symptoms only for the first two weeks of the illness

One hundred and thirty three cases of pathologically proven sCJD were identified consecutively, who met with these criteria, starting with the most recent cases (diagnosed at the end of 2002) and working backwards. Cases were included if sufficient clinical information was available for a "Patient review and examination form" to have been completed. This ensured a certain level of information was available so that direct comparisons could be made. The author and a member of the

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* Where cognitive decline is defined as memory loss, forgetfulness, confusion or disorientation and its absence was based on positive documentation (rather than the absence of comment) that it was not present according to the assessing clinician and the family.

administrative staff at the NCDJSU extracted clinical data for each of the patients identified in this group. Prior to the point in time where the more recent "Patient review and examination form" was introduced (1997) patients were not included in the Core group. This point was chosen as it was difficult for the non-medically trained researcher to interpret the written clinical histories and add the required information to the database. The information included in the database for this Core group is summarized in Table 2.1 along with the information collected for the other subgroups studied.

Data Collection

Data collection within the surveillance framework

Much of the raw data for this study was drawn from the NCJDSU archive, which had involved the work of 11 doctors* over the 12 year period, 1990-2002. The author collected data from individual cases referred from December 2001 until the end of December 2002 by visiting the patients and their families. The procedures involved in a visit are detailed below. The extraction, by the author, of specific data for this study from the NCDJSU archive shall be considered separately.

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* Robert Will, Richard Knight, Tom Esmonde, Rajith de Silva, Martin Zeidler, Gillian Stewart, Margaret-Ann MacLoed , Andrea Lowman, Colm Henry, Sarah Cooper, Craig Heath.

Assessment of suspect cases

Whenever possible all referrals categorised as Definite, Probable or Possible CJD are visited in life by a neurologist from the NCJDSU and a research nurse. A visit is only made with consent from the referring clinician, the family and, if feasible, the patient.

For patients who are not visited in life, or for those where notification came after death, a visit to the family is still undertaken whenever possible to discuss the clinical history and to collect clinical and epidemiological information. If the family or the clinician is unhappy for a visit to take place then hospital and general practitioner records are requested for review (with the consent of the family).

Collection of clinical, epidemiological and neuropathological information.

Patients and their families are visited in order to make a more detailed assessment of the clinical features of the illness and also to gain further epidemiological information and provide the family with information about CJD. A visit to assess a suspected case involves:

The completion of a "Patient review and examination form"[*] (see Appendix 3)[+]. This includes a detailed clinical history from the patients' relatives, with the addition of any further information from the medical notes. A full neurological examination is

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[*] If a patient is not seen in life then a "Late referral form" is completed with the family after death. This involves obtaining a history in the same way but relies on previous medical documentation for clinical examination findings.

[+] Efforts have been made to standardize the information gathered by the use of two proformas for the recording of clinical signs (one pre-1997, one introduced in 1997). The latter proforma allows for greater uniformity of data as symptoms and signs are specifically recorded along with their date of onset (see Appendix 3). The earlier proforma does provide an outline for the recording of clinical details although it is less structured.

carried out by the NCJDSU doctor and recorded in this form in a standardised way that ensures that the same information is collected for each patient. Information regarding clinical examination from the medical notes is added (with consent) in a separate section.

The completion, with the family, of a risk factor questionnaire as part of an ongoing case-control study.

In the majority of cases this is the responsibility of the research nurse and the questions are answered by one nominated family member (usually the next of kin).

A discussion regarding the potential diagnosis and its implications.

This would usually include giving information regarding the possibility of genetic CJD. Information produced by the CJD support network and, in cases of suspect vCJD, the Human BSE foundation is offered to the family.

With the family's consent a blood sample is taken for genetic analysis and research purposes

Copies of MRI scans and EEG recordings are requested for each patient and are then reviewed by experienced staff at the NCJDSU. EEGs are graded according to a five-point scale (normal, non-specific, suggestive, highly suggestive and typical) by one or more experienced observers blinded to the diagnosis (see Appendix 2). Each MRI scan is examined for features associated with CJD (as described in Chapter 1) or additional abnormalities, which may suggest other diagnoses. A NCJDSU doctor requests follow up information about each patient from the referring clinician. If a patient dies the NCJDSU asks to be informed of any decision regarding a post-mortem examination and any subsequent findings.

Classification.

Suspect cases are classified as CJD unlikely, Possible, Probable or Definite CJD by the NCJDSU according to current diagnostic criteria (Table 1.9). The classification may be updated as more information is gathered. The date of any change to the classification and the reasons for the change is recorded. The patient classification is noted:

1. At notification to the NCJDSU
2. When the suspect case was first seen in life by a neurologist from the NCJDSU
3. As the highest classification on the basis of clinical information alone (i.e. not including neuropathological information)
4. When review by the NCJDSU is complete (i.e. when a case file is closed)

The majority of the clinical information gathered was obtained through prospective surveillance with patients being assessed by an experienced NCJDSU observer. If a patient was notified after death then the clinical information recorded in the NCJDSU database was reliant on observations made by local medical staff. Many other studies have relied solely on retrospective information from other observers which is likely to have problems with intra observer variability and may mean that more subtle clinical signs are overlooked.

A main objective of the study was to identify and characterise defined clinical subgroups within the sCJD cohort. For the purposes of this research individual subgroups were defined (see below) and an individual case-file review was performed (by the author) on each patient. Relevant data (see Table 2.1) was extracted by the author, stored and identified by number only in Excel files to ensure confidentiality.

Applying the definition of Atypical

Those patients with an age at onset of less than 50 years and a duration of illness of two years or more were identified by an inspection of the NCJDSU database of the 485 pathologically proven cases where age and duration of illness are recorded numerically. These cases comprise the "long duration" and "young" sCJD subgroups.

Identifying clinical phenotype at presentation.

Features relating to disease presentation were identified by individual case file review. The clinical history in the 485 case files was reviewed on two separate occasions (to ensure that no cases were missed on the first review) by the author to identify presenting features. This procedure also served as a comprehensive survey of first symptoms in all pathologically confirmed sCJD cases. Each case file contains a written history (taken by an NCJDSU doctor) with emphasis placed on first symptom. In the proforma used after 1997 for each patient a separate section exists where the "first recorded symptom" is stipulated. Prior to 1997 this information is gained from the written clinical history.

Cases were identified where the first recorded symptom was visual or cerebellar*. Cases were then excluded from further analysis if a) visual onset cases had any other symptoms for the first two weeks or b) if cerebellar onset cases were documented as having symptoms of memory loss, forgetfulness, confusion or disorientation during the first month of their illness (i.e." cognitive decline").

In addition, those with another (i.e. not visual or cerebellar) focal onset were also identified if symptoms representing cognitive decline (i.e. confusion, forgetfulness, memory loss or disorientation) were absent for the first month of illness. Examples of cases with "another focal onset" would include patients whose presenting complaint was of a sensory disturbance or an involuntary movement.

It is recognised that a cognitive decline may have been present in some of these cases in the early stages but manifest in other ways (for example depression). The purpose of identifying Atypical cases in this way was to identify cases that could potentially cause diagnostic problems because they were not perceived as being cognitively impaired in the early stages. Therefore cases were not excluded from the atypical groups on the basis of psychiatric or behavioural symptoms if there was no associated cognitive decline (as defined above) and they were not perceived as being cognitively impaired.

Compiling a database for Atypical cases

Once identified each Atypical case was studied in more detail and certain clinical parameters were noted. These variables can be summarized as: clinical features, investigation results, timing of referral and clinical diagnosis in life. A breakdown of all the features noted for each case is found in Table 2.1.

Cerebral magnetic resonance imaging in Atypical cases.

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* Cerebellar symptoms were defined as gait unsteadiness, ataxia, a broad-based gait, clumsiness or falls, nystagmus or cerebellar dysarthria

The role of cerebral MRI in Atypical cases was assessed by reviewing all MR films in the NCJDSU archive on cases meeting the definition of Atypical (n=30). MRI was not included at the outset as a criteria for an Atypical case as any association with unusual clinical features is unknown. Another aspect of this study was to assess scans from clinically Atypical cases. These were matched according to within one year of scan date with scans from patients who did not possess Atypical features. This matching was done because of the variation in scan quality seen (particularly in the earlier MR sequences) as an attempt to ensure comparability of image quality. Age at onset, illness duration and the presence of specified clinical features (myoclonus, pyramidal signs, extrapyramidal signs, sensory symptoms, involuntary movements, visual symptoms/signs and cerebellar features) were noted for each patient whose scans were reviewed. Clinical features and the presence of abnormalities on the scans were assessed to look for any correlations.

Cases only notified to the NCJDSU after autopsy

A database is kept at the NCJDSU of the occupation of the individual who first notified any individual patient. Using this database all those cases were identified who were referred to the NCJDSU by neuropathologists. Those notified after death but before the results of an autopsy were known were not included in this group. Clinical data was noted for each case by a review of individual case files conducted by the author. The nature of this data is outlined in Table 2.1.

Cases classified as Possible sCJD who had not gone on to have a postmortem examination

These cases are not included in the national incidence figures for sCJD as the diagnosis remains uncertain. They are denoted here as Possible with a capital letter P to indicate they are Possible according to the diagnostic criteria rather than "it is possible they may have CJD". In life these cases were classified as Possible sCJD according to diagnostic criteria but neuropathological confirmation/ exclusion of the diagnosis was not performed. They were identified by a review of the computerised NCJDSU archive which holds data on the final classification of patients. Once the individual patients classified finally as Possible were known the author reviewed each case file and clinical data was extracted and used to compile a separate database. The data collected is summarised in Table 2.1.

Pathologically proven non-cases where CJD had been suspected in life

Patients referred to the NCJDSU with suspected sCJD between 1990 and the end of 2002 who ultimately had an alternative diagnoses proven at autopsy were identified by a review of final case classifications. Amongts these cases some were considered sufficiently likely to have CJD to warrant an assessment by an NCJDSU doctor. Cases visited in life by a NCJDSU doctor formed a group that were studied individually by retrospective case file review and were termed "clinically-selected non-cases". Clinical information was extracted as outlined in Table 2.1.

Table 2.1: Data collected for each of the subgroups in this study

Feature recorded	All sCJD	Atypical cases	Core sCJD	sCJD /vCJD group	Cases referred after autopsy	Possible sCJD	Non-sCJD (clinically selected
Final autopsy diagnosis	*	*	*	*	*		*
Age at onset	*	*	*	*	*	*	*
Age at death	*	*	*	*	*	*	*
Gender	*	*	*	*	*	*	*
Illness duration	*	*	*	*	*	*	*
sCJD suspected in life		*	*	*	*	*	*
Final classification in life		*		*	*	*	*
Presenting symptom	*	*	*	*	*	*	*
Presence of:							
Dementia		*	*	*	*	*	*
Myoclonus		*	*	*	*	*	*
Cerebellar signs		*	*	*	*	*	*
Visual disturbance		*	*	*	*	*	*
Extrapyramidal signs		*	*	*	*	*	*
Pyramidal signs		*	*	*	*	*	*
Involuntary movements		*	*	*	*	*	*
Sensory symptoms		*	*	*	*	*	*
Seizures		*	*	*	*	*	*
Psychiatric symptoms		*	*	*	*	*	*
Why sCJD suspected							*
Number of EEGs		*		*	*	*	*
Timing of EEG		*		*	*	*	*
Result of EEG(s)	*	*	*	*	*	*	*
Clinical features at EEG		*		*	*	*	*
CSF 14-3-3 result	*	*	*	*	*	*	*
MRI brain result		*		*	*	*	*
Timing of MRI brain		*		*	*	*	*
Codon 129 result	*	*	*	*	*	*	
Glycotype		*		*	*	*	
Timing of:							
specialist referral		*			*	*	
referral to NCJDSU		*			*	*	
Reasons for non referral					*		
Neurologist involved?					*	*	
Year of referral of case	*	*	*	*	*	*	*

Data Analysis

Statistical analysis was performed using Intercooled Stata version 8. Statistical advice was sought from a statistician employed by the NCJDSU.

Analyisis of Atypical cases

Clinical features.

Presenting features were documented in young and long duration sCJD cases allowing a direct comparison with those seen in sCJD as a whole in other studies. Parametric tests (Chi squared or Fisher's exact depending on the sample size) were employed to examine any statistically significant differences between symptoms at onset in these group compared with those seen in the comparison Core group of sCJD.

For each of the Atypical subgroups the proportion of patients displaying specific clinical features was calculated. For each symptom or sign the observer is asked to record its' presence as Yes, No or Not Sure on the standardised proforma used by the NCJDSU. For the purposes of this study the Not Sure values were included in the No group. Proformas used before 1997 did not include Not Sure as an option (just Yes and No).

The prevalence of specific clinical features observed throughout the illness was compared between each Atypical subgroup and the Core group. Chi squared and Fisher's exact tests were applied (depending on the sample size of the group) to assess the statistical significance of the differences observed. For each Atypical

subgroup the parameters of age and illness duration mean, median and the range were calculated. Non parametric Wilcoxon ranksum Tests (Mann Whitney U test) were applied to assess if there was a significant difference between the ages and duration of illness seen in the Atypical subgroups and the comparison Core group. By doing this the clinical phenotype of each subgroup could be established and compared with that observed in more typical sCJD (as defined by the Core group). Clinical features in the Core group were also tabulated against those seen in other studies examining clinical features in sCJD.

The age at onset and duration of illness for cases in each of the Atypical subgroups was compared graphically with the Core group using scatter plots and mathematically by employing the Wilcoxon rank sum test.

A closer examination of each long duration case of sCJD was performed. Each case file was examined thoroughly for information relating to the pattern of decline in any individual patient. Certain clinical parameters were defined as being markers of decline (onset of confusion, loss of ability to wash and dress independently, speech problems and mutism, incontinence, myoclonus, swallowing problems, immobility/becoming bed bound) and timings of the onset of problems in these areas were documented where known. This helped to gauge whether the long duration cases exhibited a generally slower overall decline or whether they declined physically at a fast rate but were sustained for long periods in a physically-dependent state.

Investigations in Atypical subgroups.

The prevalence of positive EEGs recorded amongst patients in each of the Atypical subgroups was established using defined EEG classification criteria (Appendix 2). Fisher's exact test was employed to assess differences in the prevalence of positive recordings between the Atypical groups and the Core group. The age and duration of illness in cases with positive recordings was compared with those with negative recordings using the non-parametric Wilcoxon ranksum test. The timing of the EEG recordings was tabulated.

Due to the small numbers involved and because a proportion of samples were unsuitable for analysis, CSF 14-3-3 results were not compared statistically between the subgroups. The presence of high signal in the caudate head and putamen on brain MRI was compared between cases displaying Atypical features and a comparison group matched for scan date using a Chi Squared test. The age and duration of illness of cases with high signal in these structures versus those with normal signal was compared using a Wilcoxon ranksum test.

The distribution of the genotype observed at codon 129 of the PRNP gene was compared between the Core group and each Atypical subgroup using Fisher's exact test.

Referral patterns and classfication.

The timing from disease onset to referral of cases to the NCJDSU was compared between Atypical subgroups and the Core group using the Wilcoxon ranksum test.

The proportion of cases classified as Possible, Probable and Definite was also compared between groups using Fisher's exact test.

Analysis of cases referred after autopsy

These cases were divided into those in whom the diagnosis of sCJD was suspected and those in whom it was not suspected. The clinical features were described for each group and the proportion of Atypical clinical cases amongst the groups is documented. The age and duration of illness of cases referred after autopsy is compared with that seen in cases referred before autopsy using the Wilcoxon ranksum test. The frequency and results of relevant investigations are described. The input of neurologists in diagnosis and the frequency of case referral over time is described.

Analysis of cases finally classified as Possible sCJD

The distribution of these cases over time is described along with the way that relevant investigations are utilised.

Non cases

Alternative diagnoses in this group of cases originally suspected of having sCJD are described. A clinically-selected group of cases is considered separately. Duration of disease in these cases is compared graphically with that seen in pathologically-proven sCJD cases. The clinical features of those with a final diagnosis of Alzheimer's disease are described separately.

CHAPTER 3: RESULTS

Presenting features in sCJD

Clinical data on the 485 neuropathologically proven cases of sporadic CJD known to the NCJDSU (1990-2002) were reviewed to identify the first recorded symptom. The most common presenting symptoms were those of memory loss, confusion, disorientation or forgetfulness reported in 151 (31%). Problems with gait related to unsteadiness or ataxia occur at onset in 128 (26%) of cases. When psychological and psychiatric features are combined (to include anxiety, agitation, irritability, aggression, personality change, behavioural change, depression, paranoia, hallucinations and suicidal ideation) they were present at onset in 85 (18%) of patients. There may be difficulties with some of the terms used in the case files such as "behavioural change" which could result from a problem with memory or cognition or from a psychiatric disturbance such as anxiety (factors which are often not clearly defined for each individual case). In some cases a patient presents with more than one symptom and the full results are presented in Table 3.1.

Table 3.2 compares common presenting features between studies. It should be borne in mind that other studies may have used a term such as dementia to represent not only memory loss, forgetfulness or confusion but also psychiatric features, making direct comparisons difficult.

Table 3.1: First recorded symptom in 485 pathologically proven cases of sCJD

Presenting symptom	**Number of patients** (% to nearest whole number in brackets) **N=485**
Memory loss, forgetfulness, confusion or disorientation	151 (31)
Unsteadiness/falls/ataxia	128 (26)
Visual disturbance	42 (9)
Dizziness/vertigo	38 (8)
Personality/behavioural change	33 (7)
Anxiety/irritability/aggression	31 (6)
Sensory symptoms	30 (6)
Speech problems	29 (6)
Sleep disturbance	28 (6)
Involuntary movements	26 (5)
Limb weakness	14 (3)
Depression	13 (3)
Headache	12 (3)
Handwriting difficulties	6 (1)
General slowing	6 (1)
Deafness	5 (1)
Weight loss/loss of appetite	5 (1)
Problems driving a car*	5 (1)
Paranoia	4 (<1)
Blackout/seizure	3 (<1)
Nausea/vomiting	3 (<1)
Tinnitus/earache	3 (<1)
Hallucinations	3 (<1)
Suicidal ideation	1 (<1)
Amnesic episode	1 (<1)
Information regarding disease onset unavailable	7 (1)

* Two cases were involved in minor accidents, two cases became lost whilst driving and one had difficulty coordinating the car's controls

Table 3.2 A comparison of presenting features in sCJD between this study and six other studies where n>100 (expressed in percentages)

	This study (n=485)	Brown et al, 1979 [67] (n=124)	Will & Matthews, 1984 [64] (n= 137)	Brown et al, 1986 [69] (n=230)	Brown et al, 1994 [13] (n=232)	de Silva, 1998 [88] (n=144)	Lundberg, 1998 [16] (n=122)
% pathologically confirmed	100	100[a]	77[a]	100[a]	>95	84	58
Memory loss, confusion, disorientation or forgetfulness	31						
Memory loss					48		
Dementia		29	21	31		61	50
Ataxia/cerebellar	26	29	19	34	33	39	48(inc. vertigo)
Visual disturbance	9	17	9		19	10	
Oculomotor				6			
Other visual problem				14			
Vertigo/dizziness	8	8	11	7	13		
Speech disturbance	6		5 (inc dysgraphia)			4	10 (inc apraxia)
Headache	3	10	3	7	11		
Sensory	6	2	4	5	6	3	4
Blackout/seizure	<1		1	<1	0		
Involuntary movements other than myoclonus	4	1	5	<1	4	1	2

[a] These studies include between four and ten percent familial cases

"Atypical" sCJD

Atypical cases shall be considered under the following headings:

Young cases	(with an age at onset of less than 50 years)
Long duration cases	(with a duration of illness of greater than or equal to two years)
Pure visual onset cases	(cases with reported visual symptoms *only* for the first two weeks of the illness)
Cerebellar onset cases	(those presenting with a cerebellar syndrome in the absence of cognitive decline (i.e. memory loss, forgetfulness, confusion or disorientation for at least one month into the illness)
Other focal onsets	(those with symptoms other than cognitive decline, or those defined above, for at least the first month of the illness)

Comparing Atypical sCJD to sCJD without Atypical features ("Core sCJD")

In order to make comparisons between clinical features seen in typical cases and those seen in other cases of sCJD a group of patients were selected to represent a Core group of sCJD. This group comprised of one hundred and thirty three consecutive cases of pathologically proven sCJD without defined Atypical features (working chronologically backwards from the end of 2002). The mean age at onset in this core group was 69 years (median 69 years, range 50-94 years) and the mean duration of illness was 5.5 months (median 4 months, range 1-22 months). By

definition the patients had to be fifty or more years old and have a disease duration of less than two years.

The clinical features present in this group are summarized in Table 3.3 and a comparison is made with the incidence of features seen in cases in other large studies in Table 3.4. As any case with Atypical features (as defined by our study) has been excluded, the comparison with other studies is limited (as these would have not excluded unusual cases). Visual symptoms for example are less common in the Core group when compared with some other studies, which is likely to reflect the exclusion of any cases with a pure visual onset.

Table 3.3: Percentages of patients in the Core group of sCJD (n=133) displaying selected clinical features

Clinical feature	%
Myoclonus	85
Cerebellar signs	77
Pyramidal signs	64
Extrapyramidal signs	42
Psychiatric symptoms	37
Involuntary movements	27
Dizziness/vertigo	26
Visual disturbance	24
Sensory symptoms	10
Seizures	9

Table 3.4: Clinical features present throughout the illness in a Core group (n=133) of sCJD and seven other studies where n>100

	Core SCJD: this study n=133	Brown et al, 1979 [67] n=124	Will & Matthew 1984 [64] n=137	Brown et al, 1986 [69] n=230	Brown et al, 1994 [13] n=232	de Silva, 1998 [88] n=144	Lundberg, 1998 [16] n=122	Poser et al, 1999 [92] n=201
% PM proven	**100**	100[a]	77[a]	100[a]	>95	84	58	51
Memory loss, confusion, forgetfulness or disorientation	**100**							
Dementia		94	100	96			100	96
Memory loss					100	64		
Disorientation						78		
Ataxia			62				80	86
Cerebellar signs	**77**	56	42	61	71			
Incoordination						85		
nystagmus						20		
Myoclonus	**85**	84	82	88	78	85	75	89
Other mvt disorder	**27**	32		26	36		53	
Chorea						13		
dystonia						16		
Visual	**24**	40		42	42			
Disturbance			33				18	54
Hallucinations			17	16		32	25	
Blindness			13			52		
oculomotor						27	28	
Pyramidal signs	**64**	44	79 (inc *rigidity*)	43	62	62		52
Extrapyramidal	**42**	60	3	67	56			73
Rigidity						38		
Parkinsonism						34		
Sensory disturbance	**10**	7			11		16	
Seizures	**9**	9	9	8	19	13	28	12

[a] These studies include between four and ten per cent familial cases

Clinical features of Atypical cases

One hundred and fifteen patients (24%) out of 485 pathologically proven cases of sCJD met one or more of the criteria for an Atypical case. The proportion of cases in each Atypical subgroup is displayed in Figure 3.1. Eighteen patients (four per cent) met with the definition of more than one category (e.g. young with a long duration of illness) and the overlap of Atypical features displayed by these patients is summarized in Figure 3.2. There were 55 men and 60 women (male to female ration of 1.0 : 1.1) who had one or more Atypical feature. The mean age at onset in the total Atypical group was 58 years (range 15-88 years) and the mean duration of illness was 13.3 months (range 2-74 months). The combined total of all the Atypical subgroups is 133 (18 patients appear in more than one group).

Figure 3.1: Numbers of patients in Atypical subgroups and sCJD as a whole (1990-2002)

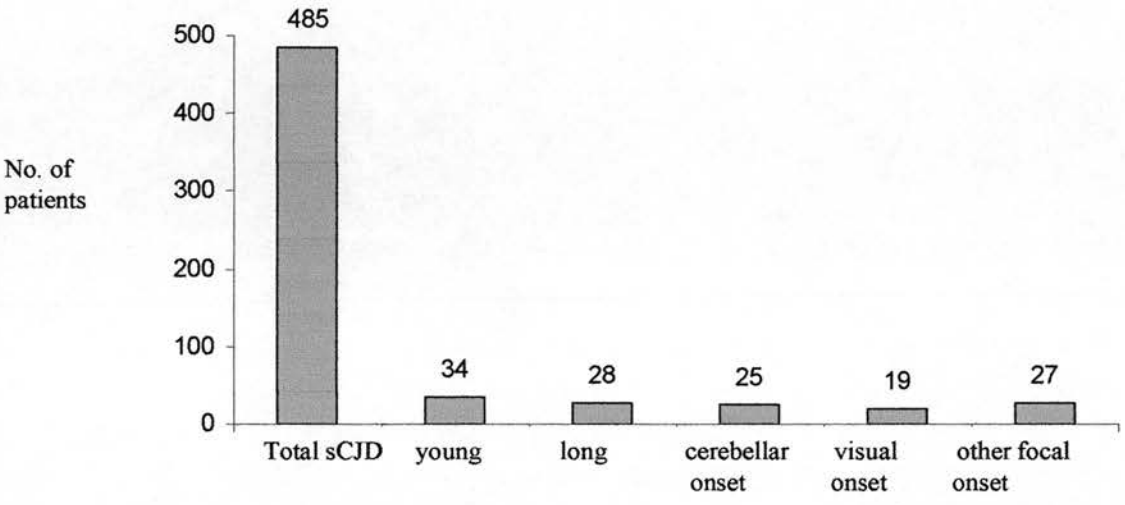
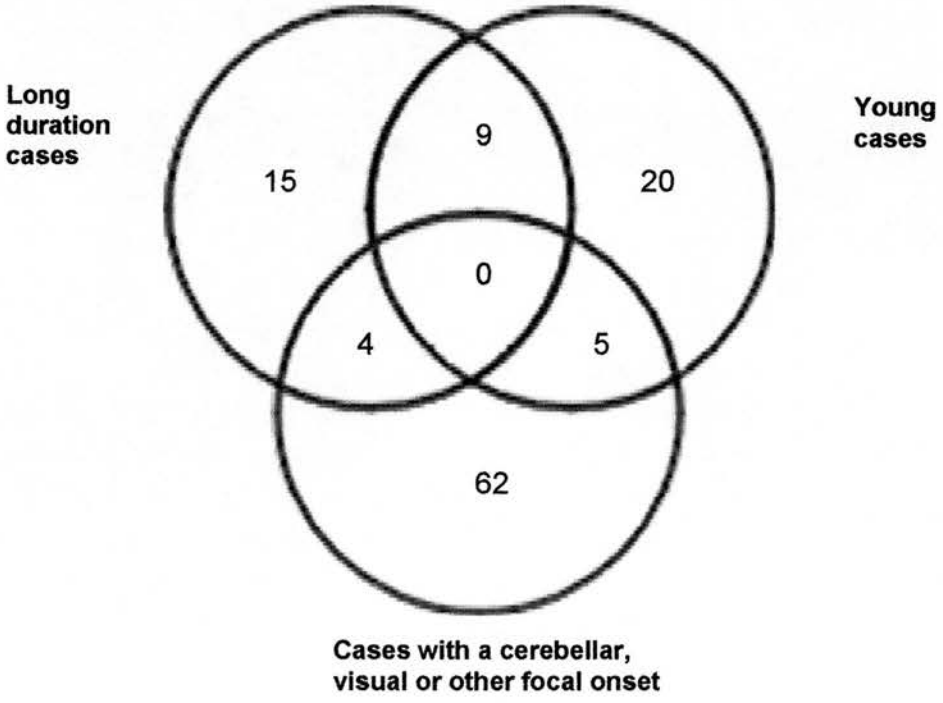


Figure 3.2: Venn diagram displaying the overlap with cases that possess more than one Atypical feature (n=18)



(The numbers in each section indicate the number of patients)

Young cases.

A young case of sCJD is defined, for the purposes of this study as a patient with pathologically proven sCJD whose first symptom was recorded below the age of 50. Thirty four patients out of 485(seven per cent) fell into this category.

Sixteen of the patients were male, 18 were female. The mean disease duration in this group was 18.7 months (median 11 months, range 2-60 months). The age distribution amongst young cases is summarized in Table 3.5 (two cases occurred under the age of 30 years). Duration of illness was not compared directly with the Core sCJD group as these all had disease durations of less than two years by definition. One patient is not included in any further analysis, as the case notes were unavailable at the time of this study. PRNP gene mutation analysis (excluding genetic CJD) was performed in 27/34 (79%).

Table 3.5: Age distribution of young cases

Age range (years)	Number of patients (total =33)
< 15	0
15-20	1
21-25	1
26-30	0
31-35	0
36-40	4
41-45	10
46-50	17

The first observed symptoms in the young cases are summarized in Table 3.8 and a comparison is made with those seen in Core sCJD. It is less common for young

cases to present with unsteadiness/falls/ataxia compared with Core sCJD (p=0.028, Fisher's exact test). It is more common for the younger patients to present with personality/behavioural change when compared with Core sCJD (p=0.0015, Fisher's exact test). There was no statistically significant difference between other presenting features amongst young and Core sCJD cases.

The proportions of young patients with specific clinical features throughout the illness are summarized in Table 3.6. Young cases, when compared with the Core group (n=133), were more likely to exhibit psychiatric features (p=<0.001, chi squared test) and involuntary movements other than myoclonus (p=0.016, chi squared test) during the course of the illness. Young cases were less likely to display cerebellar features (p=0.004, chi squared test) and extrapyramidal signs (p=<0.001, chi squared test) than those in the Core group. These features and those seen in other Atypical groups when compared with the Core group are summarized in Table 3.7.

Table 3.6: Clinical features in young cases

Clinical sign	% (n=33)
Myoclonus	94
Pyramidal signs	79
Psychiatric symptoms	79
Cerebellar signs	52
Involuntary movements	48
Visual disturbance	39
Sensory disturbance	21
Dizziness/vertigo	15
Extrapyramidal signs	9
Seizures	9

Table 3.7: Statistically significant differences between clinical features seen through the course of the illness in Atypical sCJD subgroups versus Core sCJD (n=133)

(using chi squared test except where indicated)

Clinical subgroup	Clinical features seen more often than in Core sCJD	P value	Clinical features seen less often than in Core sCJD	P value
Young	Psychiatric features	<0.001	Cerebellar signs	0.004
	Involuntary movements (other than myoclonus)	0.016	Extrapyramidal signs	<0.001
Long	Psychiatric features	<0.001	Cerebellar signs	0.014
			Extrapyramidal signs	0.031
Pure cerebellar onset	Visual disturbance	<0.001		
	Psychiatric features	0.0012		
	Sensory symptoms	0.008✧		
Pure visual onset			Extrapyramidal signs	0.002✧
			Cerebellar signs	0.0011✧
Other focal onset associated with a delay in the onset of cognitive decline	Sensory disturbance	<0.001	Extrapyramidal signs	0.002
	Psychiatric symptoms	0.013	Cerebellar signs	0.008
	Involuntary movements	0.010		

✧Fisher's exact test

Long duration cases.

Long duration sCJD is defined in this study as a pathologically proven case of sCJD with a disease duration of greater than or equal to two years. Twenty eight patients out of 485 (six per cent) with pathologically proven sCJD died two years or more after disease onset. Three patients were alive at the time of the study therefore their disease duration is, as yet, unknown. Therefore 28/482 (6%) of sCJD patients had a disease duration greater than or equal to 24 months*. This is illustrated in Figure 3.3.

The mean age at onset in this group was 54 years (median 54 years) with a range of 15 years to 75 years. Thirteen of the patients were men and fifteen were women. PRNP gene mutation analysis (to exclude genetic CJD) was performed in 15/28 (54%). None of the remainder had a family history of CJD.

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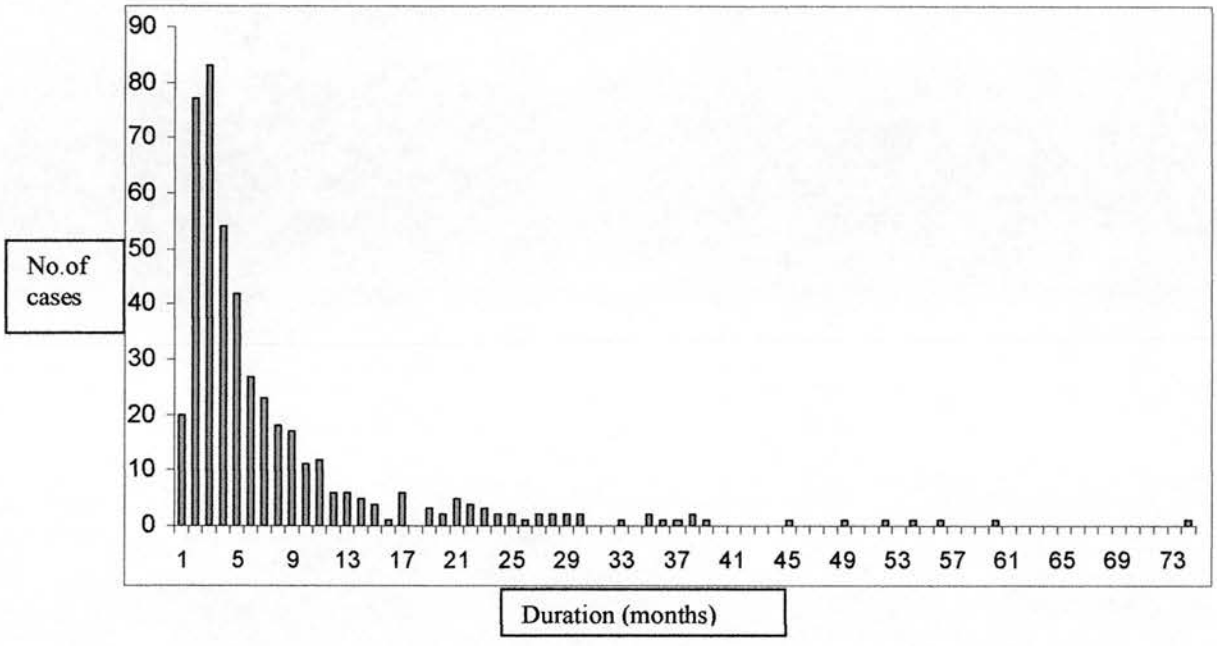
* Illness duration was not documented to the nearest month in 14 cases. This was often due to a lack of precise information as to disease onset or date of death. However, on review of these case notes it was possible to establish that none of these cases had a disease duration of greater than (or equal to) two years.

Figure 3.3: Distribution of illness duration in pathologically proven sCJD



(Cases are included where disease duration was known to the nearest month (n=468))

Presenting features in long duration cases are compared with those seen in the Core group of sCJD in Table 3.8. Personality or behavioural changes are more common at onset in long duration cases than in other sCJD (p = 0.002, Fisher's exact test) as is depression (p=0.037, Fisher's exact test). Unsteadiness, falls or ataxia are less common at onset in the long duration cases (p=0.04, chi squared test,). The proportions of long duration cases with specific clinical features throughout the whole illness are summarized in Table 3.9. Long duration cases are compared with the Core group of sCJD (n=133) and are more likely to exhibit psychiatric symptoms (p=<0.001, chi squared test). They are less likely to display extrapyramidal signs (p=0.03, chi squared test) or cerebellar signs (p=0.014, chi squared test) throughout the course of the illness (see Table 3.7) when compared with the Core group.

Table 3.8: Presenting features in young and long duration sCJD compared with sCJD as a whole (percentages to the nearest whole number in brackets).

Presenting symptom	Young cases (n=33)		Long duration sCJD (n=28)		Core sCJD (n=133)		*Total sCJD (n=485)*	
Cognitive decline (memory loss, confusion, disorientation)	11	(33)	15	(54)	56	(42)	*151*	*(31)*
Unsteadiness/falls/ataxia	2	(6)	2	(7)	31	(23)	*128*	*(26)*
Visual disturbance	1	(3)	0		6	(5)	*42*	*(9)*
Dizziness/vertigo	1	(3)	0		11	(8)	*38*	*(8)*
Anxiety/irritability/aggression	5	(15)	4	(14)	9	(7)	*31*	*(6)*
Sensory symptoms	3	(9)	1	(4)	2	(1)	*30*	*(6)*
Speech problems	3	(9)	1	(4)	12	(9)	*29*	*(6)*
Sleep disturbance	1	(3)	3	(11)	3	(2)	*28*	*(6)*
Involuntary movements	2	(6)	1	(4)	4	(3)	*26*	*(5)*
Personality/behavioural change	4	(12)	5	(18)	2	(1)	*19*	*(4)*
Limb weakness	0		0		3	(2)	*14*	*(3)*
Depression	3	(9)	3	(11)	2	(1)	*13*	*(3)*
Headache	1	(3)	0		1	(<1)	*12*	*(3)*
Handwriting difficulties	1	(3)	0		2	(1)	*6*	*(1)*
General slowing when performing daily activities	2	(6)	1	(4)	2	(1)	*6*	*(1)*
Withdrawal/loss of interest	1	(3)	0		2	(1)	*5*	*(1)*
Deafness	0		0		0		*5*	*(1)*
Weight loss/loss of appetite	1	(3)	0		2	(1)	*5*	*(1)*
Problems driving a car	0		1	(4)	2	(1)	*5*	*(1)*
Paranoia	0		1	(4)	1	(<1)	*4*	*(<1)*
Blackout/seizure	1	(3)	0		1	(<1)	*3*	*(<1)*
Nausea/vomiting	1	(3)	0		1	(<1)	*3*	*(<1)*
Tinnitus/earache	1	(3)	0		0		*3*	*(<1)*
Hallucinations	0		0		2	(1)	3	(<1)
Suicidal ideation	0		0		0		*1*	*(<1)*
Amnesic episode	0		0		1	(<1)	*1*	*(<1)*
Information re. onset unavailable	1	(3)	1	(4)	2	(1)	*7*	*(<1)*

Table 3.9: Clinical features in long duration sCJD

Clinical sign	% (n=28)
Psychiatric features	82
Myoclonus	68
Pyramidal signs	54
Cerebellar signs	46
Involuntary movements	39
Sensory symptoms	21
Extrapyramidal signs	21
Visual disturbance	18
Dizziness/vertigo	7
Seizures	4

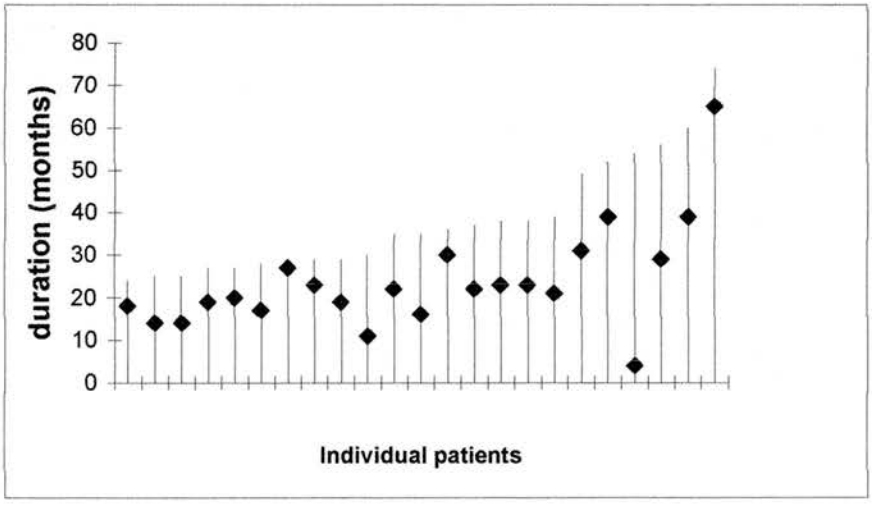
Seven of these patients (25%) were still able to walk at 24 months. Only two of the 28 patients had lost the ability to walk before one year (one at four months and one at 11 months). Five out of the 28 patients in this group (18%) still had some degree of speech at 24 months. Clinical parameters are recorded, where known, according to their presence/absence at six monthly intervals and summarized in Table 3.10. Figure 3.4 illustrates how far into the illness individuals developed problems with gait and when they were last recorded as walking (their ability to walk may have continued beyond this point and not been recorded in some cases). In most cases of sCJD (with death occurring within six months) gait disturbance is prominent and early. The long duration cases seen here have, with one notable exception*, a genuinely slower disease progression rather than a rapid progression with many months of being sustained in an akinetic and mute state.

* In one highly unusual case the patient was akinetic, mute and bed bound by four months but lived for a total of 54 months. This patient was also the youngest patient in our series (15 years old at disease onset).

Table 3.10: The progression of clinical features in sCJD of long duration (n=28)

	TIME SINCE ILLNESS ONSET (MONTHS) WHEN SYMPTOM EMERGED						
CLINICAL FEATURE	0-6	7-12	13-18	19-24	>24	Unsure	Total no. of patients
	Number of patients						
Confusion/ forgetfulness	21	4	0	0	0	3	28
Unable to wash/dress	2	4	6	4	3	9	28
Became bed bound	1	1	3	7	7	9	28
Developed incontinence	1	0	4	4	4	15	28
Developed myoclonus	1	2	3	4	5	13	28
Speech problems first noted	9	1	6	2	3	7	28
Became mute	1	1	2	3	5	16	28
Developed swallowing problems	1	0	2	3	7	15	28

Figure 3.4: Duration of illness and timing of immobility in 23 long duration cases
Illness duration is represented by the vertical line, in cases where information regarding time when last being able to walk (♦) was recorded



Cases presenting with a cerebellar syndrome in the absence of early cognitive decline.

These cases were defined as individuals presenting with features of cerebellar dysfunction in the absence of any documented memory loss, confusion forgetfulness or disorientation for at least one month from symptom onset. Twenty five (five per cent) of the 485 patients met with this definition. Although 26% of the total sCJD cohort presented with unsteadiness or ataxia this was also often associated with an early decline in cognition and therefore not included here.

There were seventeen men and eight women. The mean age at onset was 64 years (median 62 years, range 48 to 76 years). The mean duration of illness was 9.5 months (median 8 months, range 2-36 months). All but one were aged over 50 years of age at disease onset. PRNP gene mutation analysis (to exclude genetic CJD) was performed in 14/25 (56%). None of the remainder had a family history of CJD.

The predominant early features of the illness were of unsteadiness and poor coordination in all. The very first documented symptoms were of gait unsteadiness in 17, dizziness in five and poor coordination in two. In three of the 25 (12%) there were associated sensory symptoms at presentation (burning sensations in the left upper and lower limbs in one and parasthaesia in the back in two). Two also had visual symptoms at onset (one blurred vision, one double vision), one also complained of headache and one of excessive tiredness. The proportions of patients with specific clinical features throughout the whole illness are summarized in Table 3.11. When compared with the Core sCJD group

these patients were found to be more likely to exhibit visual disturbance (p=<0.001, chi squared test), sensory symptoms (p=0.008 Fisher's exact test) and psychiatric symptoms (p=0.0012, chi squared test) (see Table 3.7).

Table 3.11: Clinical features in cerebellar onset cases

Clinical features	% (n=25)
Cerebellar signs	100
Pyramidal signs	86
Myoclonus	72
Psychiatric features	64
Visual disturbance	60
Dizziness/vertigo	48
Extrapyramidal signs	44
Involuntary movements	36
Sensory symptoms	32
Seizures	4

Cases presenting with isolated visual symptoms.

This group was composed of patients presenting with pure visual symptoms that persisted for at least two weeks into the illness in isolation (i.e. with no other documented symptoms or signs).

Nineteen patients out of 485 (4 per cent) met this definition and were included in this group. Seven of these patients were men and 12 were women. The mean age at onset was 67 years (median 65 years, range 50-88 years). The mean duration of illness was 4 months (median 3 months, range 1-17 months). Fifteen (79%) patients had an illness duration of 3 months or less. Disease duration was more likely to be shorter in the pure visual onset group than that observed in Core sCJD (p=0.015, Wilcoxon rank sum test) despite the fact that the Core group excluded long duration cases by

definition. PRNP gene mutation analysis (to exclude genetic CJD) was perfomed in 13/19 (68%).

The most common visual disturbance was of worsening visual acuity (although blurred vision, visual distortions, visual field loss, dyschomatopsia, visual delusions and palinopsia are also described) (see Table 3.12). The proportions of patients with specific clinical features throughout the whole illness are summarized in Table 3.13. When compared with a core sCJD group these patients were less likely to exhibit extrapyramidal signs ($p=0.002$, Fisher's exact test) and cerebellar features ($p=0.0011$, Fisher's exact test) (see Table 3.7).

Table 3.12: Description of visual symptoms at onset in pure visual onset cases

Symptom at onset	No of patients (total n=19)
Worsening visual acuity	7
Blurred vision	5
Visual distortions	4
Visual field loss	2
Disturbance of colour vision	1
Visual delusions/hallucinations	1
Palinopsia	1

Table 3.13: Clinical features in pure visual onset cases

Clinical features	%
Visual disturbance	100
Myoclonus	95
Pyramidal signs	84
Cerebellar signs	47
Psychiatric features	32
Involuntary movements	28
Sensory disturbance	17
Extrapyramidal signs	6
Seizures	0
Dizziness/vertigo	0

Cases presenting with other focal symptoms and a delay in the onset of cognitive dysfunction.

This group comprised of cases presenting with focal features (excluding a pure cerebellar syndrome or isolated visual problems as these are considered separately) and no documented memory loss, forgetfulness, confusion or disorientation for at least one month. Included in this group were ten patients who presented with psychiatric symptoms*. It is recognised that these symptoms may be early features of a dementia but they have been included here as, in the absence of memory loss, forgetfulness, confusion or disorientation they were considered to represent a psychiatric phenomenon by the involved clinicians. Twenty seven patients (6 per cent) were found who clearly met with this definition according to the available documentation. Cases were not included where the presence or absence of a

* Defined as depression, anxiety, apathy, withdrawal, delusions (these characteristics are the same as those listed in the vCJD diagnostic criteria)

cognitive decline was ambiguous. Presenting features in this group are summarized in Table 3.14.

Seventeen of these patients were women and 10 were men. The mean age at disease onset in this group was 61 years (median 65 years, range 43-78 years) with a mean disease duration of 11 months (median 10 months, range 2-30 months). Three of the patients in this group were also in the long duration subgroup (duration of illness being 29, 30 and 24 months) and three were under the age of 50 years at disease onset. One patient, who had been diagnosed by cerebral biopsy, was alive at the time of writing nearly two years into the illness. PRNP gene analysis (to exclude genetic CJD) was performed in 12/27 (44%).

Table 3.14: Presenting features in the "other focal onset" group (n=27)

NB. There may be more than one symptom at onset

Symptom	No. of patients
Sensory disturbance	**15 (56%)**
Upper limb pain	1
Upper limb numbness	4
Upper limb parasthaesia	3
Lower limb pain	3
Lower limb numbness	1
Lower limb parasthaesia	3
Psychiatric symptom	**10 (37%)**
Depression	4
Anxiety	3
Irritability	2
Aggression	1
Involuntary movement	**6 (22%)**
Chorea	2
Dystonia	2
Tremor	1
"restless legs"	1
Limb weakness	2
Deafness	1
Vertigo	1
Weight loss	1

This group also includes three unusual cases that developed a progressive quadraparesis. They each complained of early and persistent sensory features: burning dysasthaesia in the feet in one, pins and needles in the left upper and lower limbs in the second and persistent, severe discomfort in the joints (for

which no rheumatological cause was found) in the third. Unfortunately although all three had a neuropathological examination (two an autopsy and one a brain biopsy) tissue from the peripheral nervous system was not examined. A diagnosis of sCJD was only made in life in the case who underwent cerebral biopsy.

The presence of specific clinical features throughout the illness in the focal onset group is summarized in Table 3.15. When compared with the consecutively selected Core group of sCJD patients (n=133) these patients were more likely to have sensory symptoms (p=<0.001, chi squared test), involuntary movements (p=0.01, chi squared test) and psychiatric symptoms (p=0.013, chi squared test). Extrapyramidal signs were less common (p=0.002, chi squared test) as were cerebellar signs (p=0.008, chi squared test). These results and those from the other Atypical subgroups are summarized in Table 3.7.

Table 3.15 Clinical features in the other focal onset group (n=27)

Clinical feature	%
Myoclonus	81
Pyramidal signs	74
Sensory disturbance	70
Psychiatric features	63
Cerebellar signs	52
Involuntary movements	52
Visual disturbance	41
Extrapyramidal signs	11
Seizures	7
Dizziness/vertigo	7

Summaries of ages at onset and disease duration in the Atypical subgroups compared with Core sCJD and total sCJD are to be found in Figures 3.5 and 3.6. Table 3.16 summarizes the male to female ratios amongst the subgroups.

Table 3.16: Male to female ratio in atypical subgroups

	Male: female
Young cases (n=34)	16:18
Long duration cases (n=28)	13:15
Cerebellar onset cases (n=25)	17:8
Pure visual onset cases (n=19)	7:12
Other focal onset cases (n=27)	10:17

Figure 3.5: Scatter plot showing age at onset in Core sCJD, total sCJD and Atypical subgroups

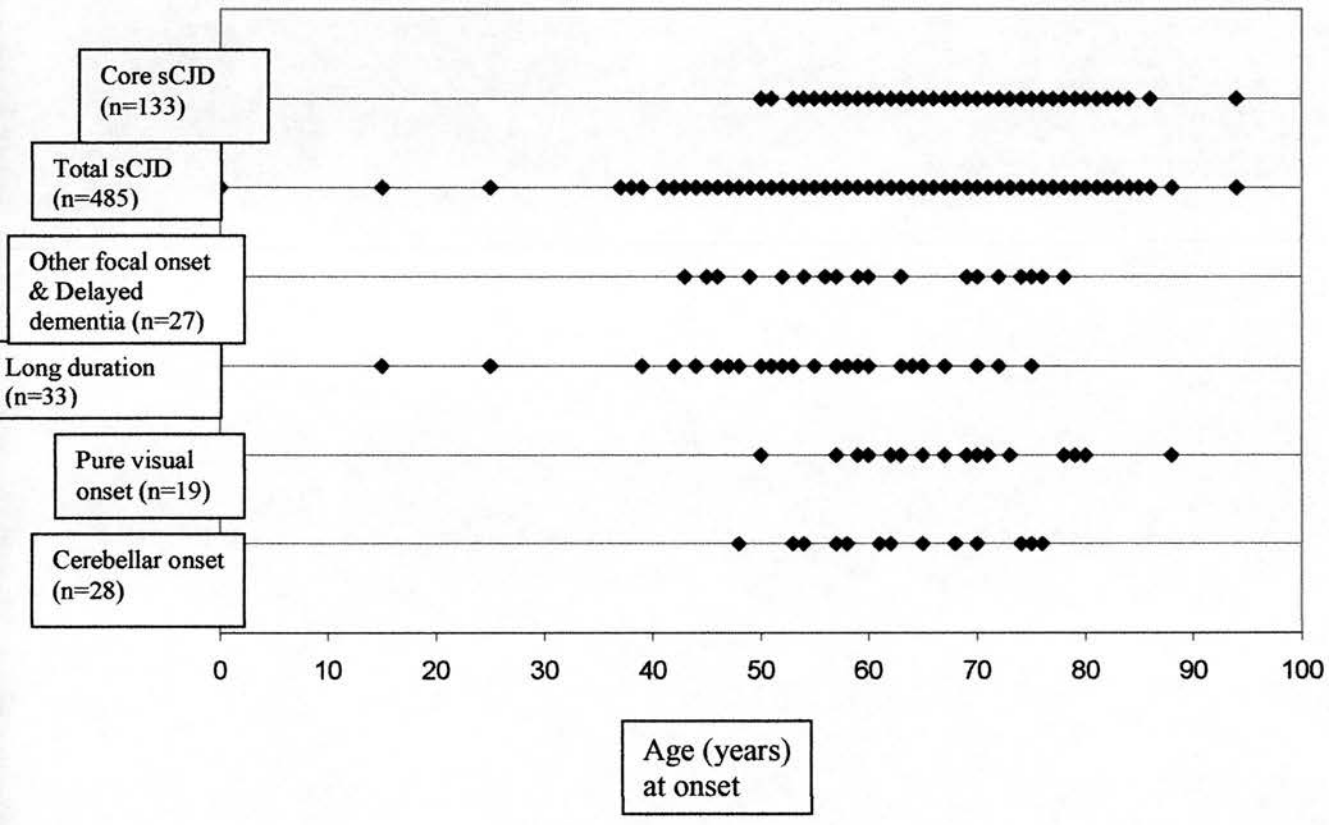
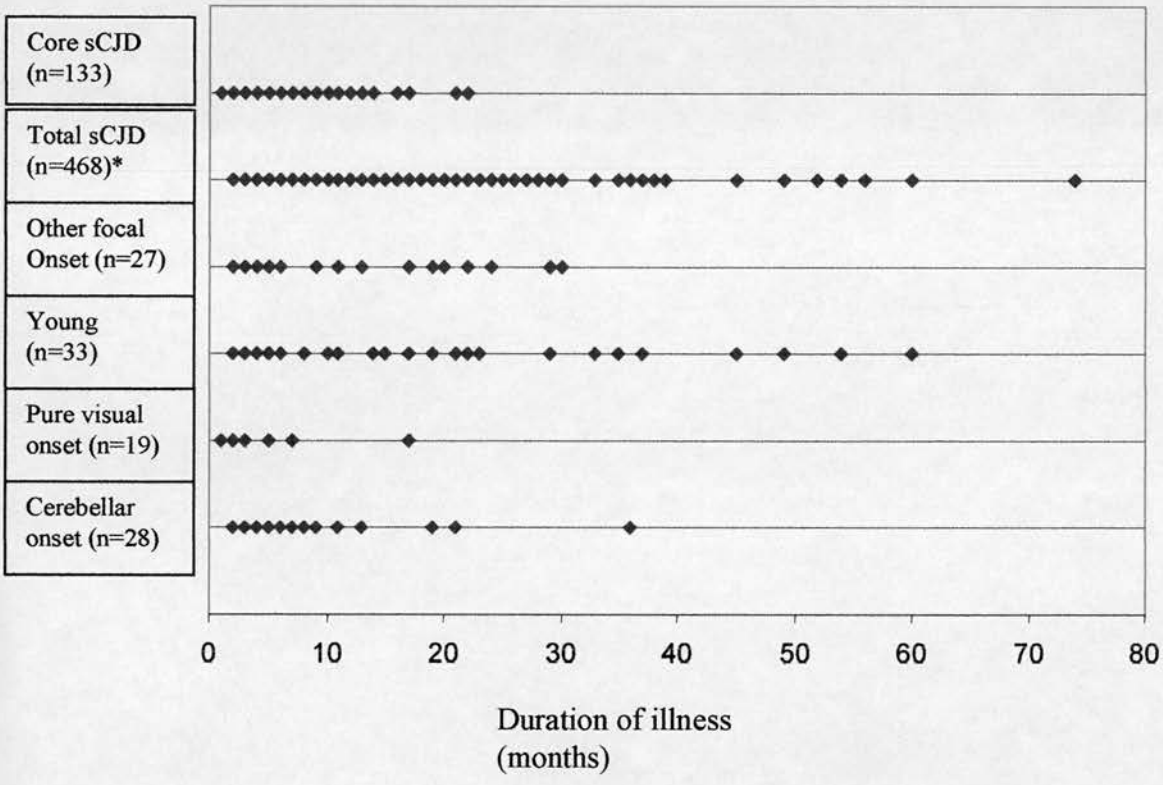


Figure 3.6: Scatter plot showing duration of illness in core sCJD, total sCJD and Atypical subgroups

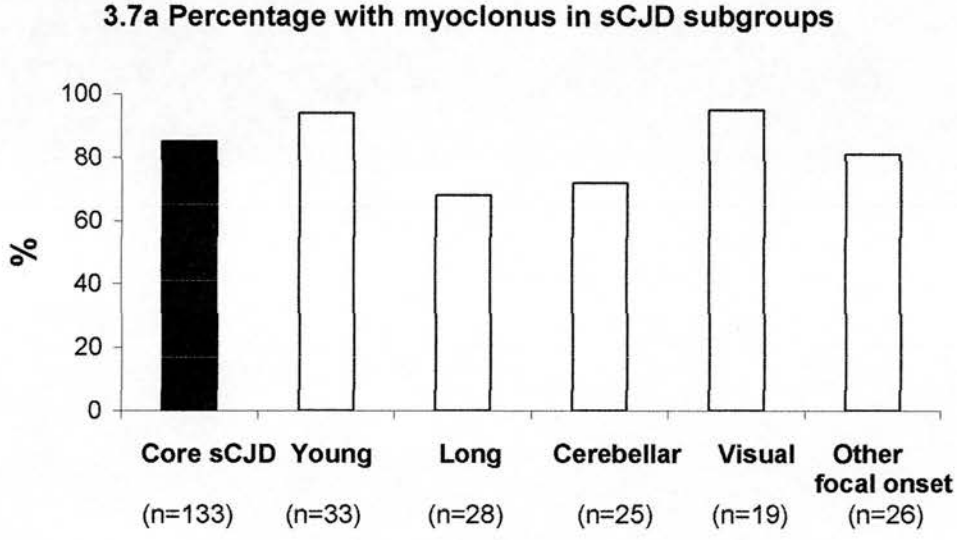
(excluding long duration sCJD who by definition have a duration of illness of ≥ two years)

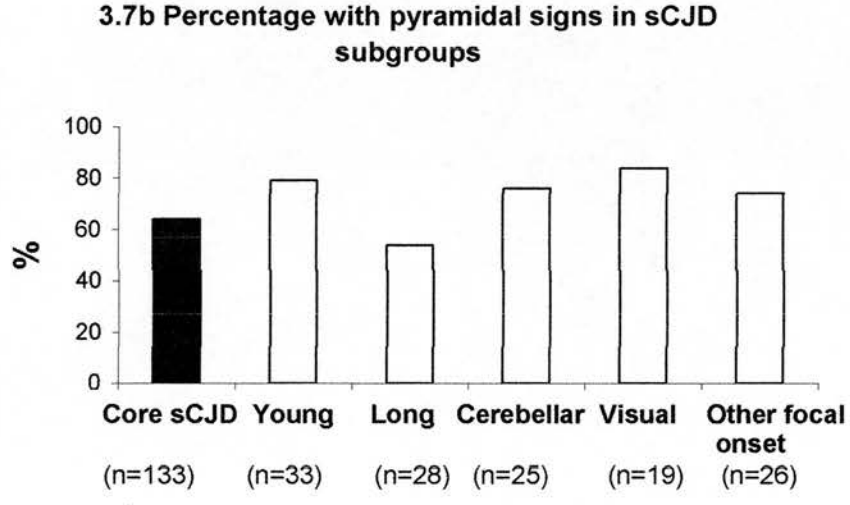


* where illness duration known to the nearest month

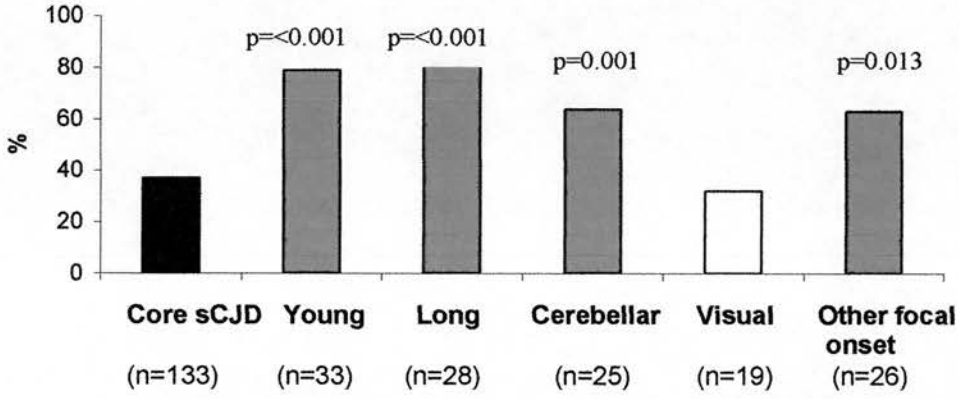
Differences between clinical features observed in the Atypical subgroups and Core sCJD are summarized in Figure 3.7. The columns highlighted in red indicate subgroups where there was a statistically significant difference ($p<0.05$) in the prevalence of the symptom or sign when compared to the core sCJD cohort. Columns filled with grey indicate subgroups where the clinical feature in question will be present by definition e.g. visual symptoms in the pure visual onset group).

Figure 3.7: Clinical symptoms and signs in Atypical sCJD subgroups compared with the core sCJD group

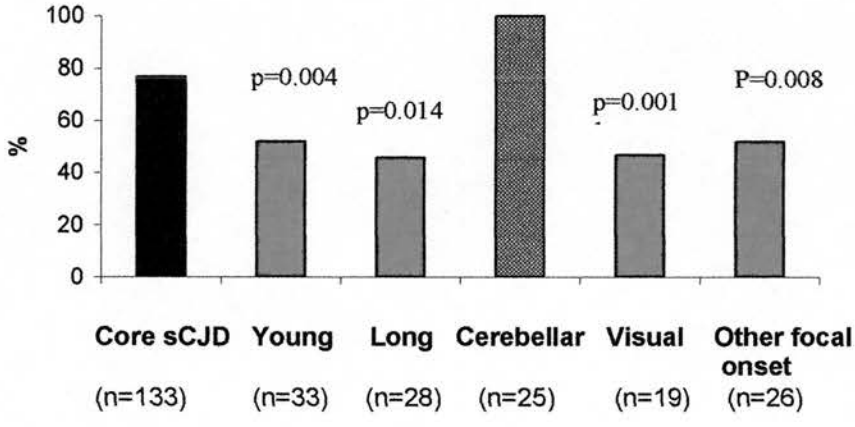




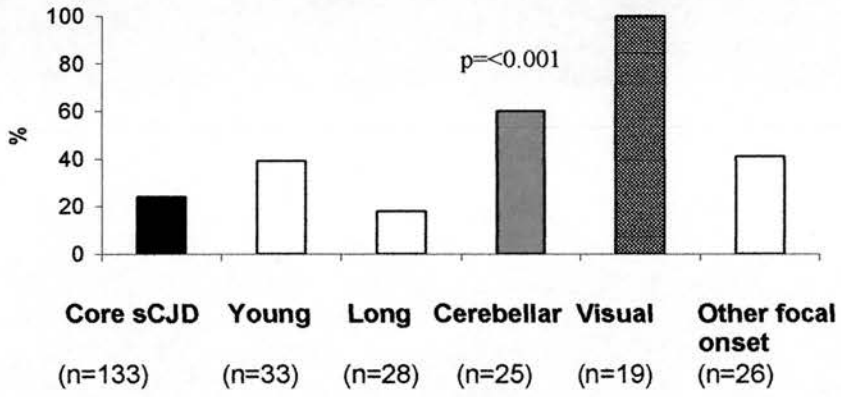
3.7 c Percentage with psychiatric symptoms in sCJD subgroups



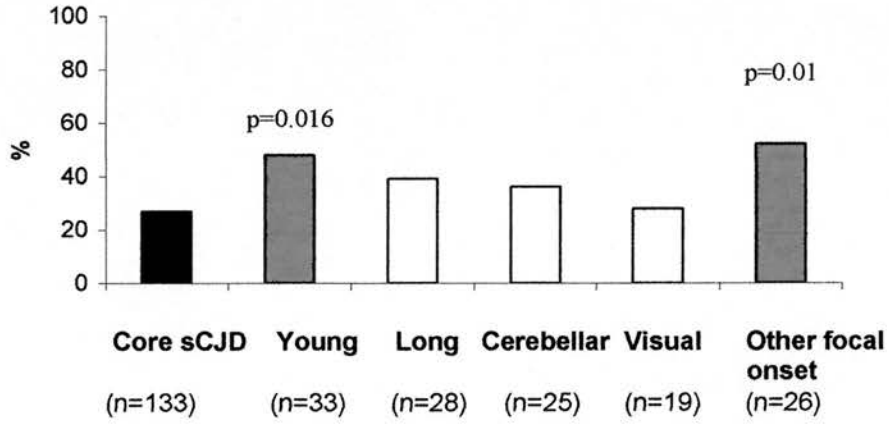
3.7d Percentage with cerebellar signs in sCJD subgroups



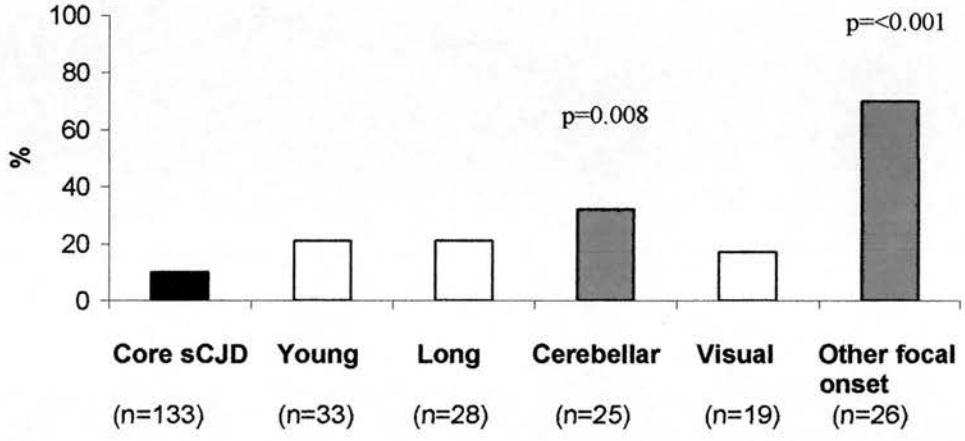
3.7f Percentage with visual disturbance in sCJD subgroups



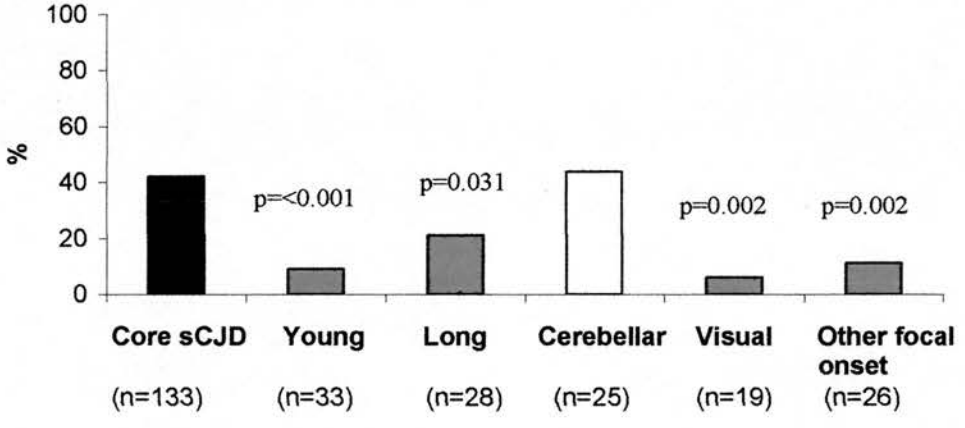
3.7e Percentage with involuntary movements (other than myoclonus) in sCJD subgroups



3.7g Percentage with sensory disturbance in sCJD subgroups



3.7h Percentage with extrapyramidal signs in sCJD subgroups



Investigations in Atypical cases

The EEG in Atypical sCJD.

One hundred and five patients with Atypical features (89% of the total Atypical group) had an EEG. Seventeen patients (16%) had an EEG that showed characteristic periodic sharp wave complexes. In order to limit confusion from now on this shall be referred to as a "positive" EEG (which equates to the criteria for a "typical" EEG used in Appendix 2). The proportion of positive EEGs was highest in the pure visual onset group (39%). This is an equivalent level to that witnessed in sCJD as a whole within the UK surveillance system (where 416 out of the 485 pathologically proven cases had an EEG and 162 of these were regarded as positive) (NCJDSU data). None of the long duration cases that had an EEG (n=22) displayed a positive recording. The distribution of these positive recordings amongst the subgroups is illustrated in Figure 3.8. Compared with the Core group (where 35/104 (34%) of final EEG recordings were positive) young cases, long duration cases and pure cerebellar onset cases were significantly less likely to exhibit a positive EEG ($p=0.018$, $p=<0.001$ and $p=0.025$ respectively, Fisher's exact test).

The mean age at onset within the positive EEG group was 63 years (range 43-78 years) compared with 57 years in the Atypical cases with a negative EEG (see Figure 3.9). A positive EEG was significantly associated with an older age at disease onset ($p=0.038$, Wilcoxon rank sum test) amongst the clinically Atypical cases. Atypical cases with a positive EEG had a mean duration of illness of 4 months (range1-9 months) compared with a mean duration of 17 months in the Atypical cases with a negative EEG. The distribution of disease duration in these Atypical cases with EEG recordings is illustrated in Figure 3.10. A positive EEG was significantly associated

with a shorter disease duration (p=<0.001, Wilcoxon rank sum test) amongst the clinically atypical cases. Fifteen out of the 17 with a positive EEG had documented myoclonus at the time of the recording (88 per cent). In two cases the clinical details regarding the presence or absence of myoclonus were unclear. Fourteen out of 17 were bed bound at the time of the EEG (82 per cent) with only one patient clearly documented as still being mobile. Codon 129 genotype was known in seven out of the seventeen and all were MM (four MM1, three glycotype unknown). Figure 3.11 illustrates the timing of the EEG in terms of proportion of illness passed.

Figure 3.8: Percentage of positive EEGs in sCJD compared with Atypical subgroups

(numbers above columns indicate number of patients within each subgroup who had an EEG recording)

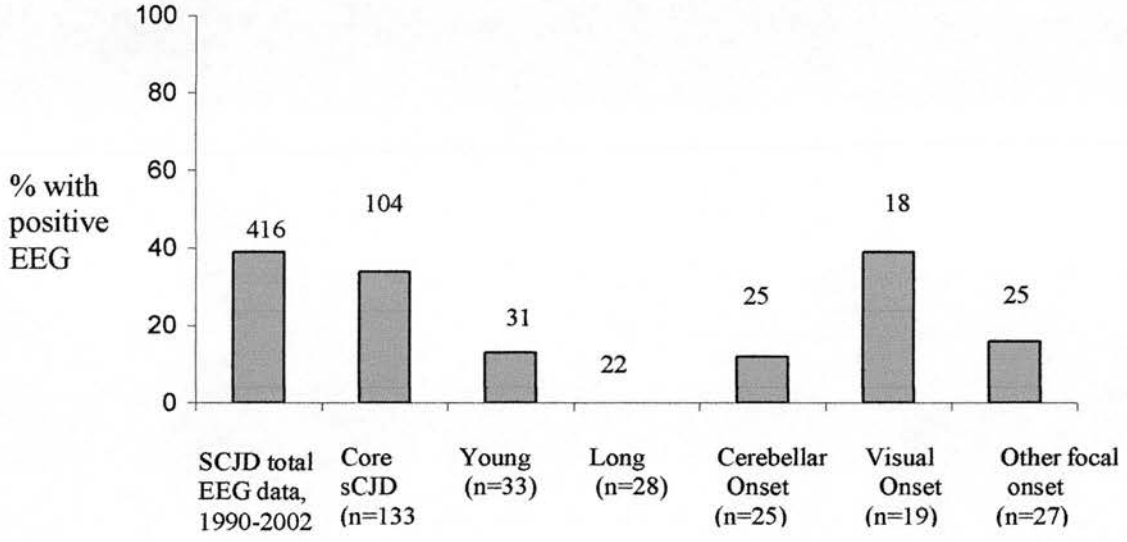


Figure 3.9: Age at disease onset of Atypical sCJD cases with positive EEGs (n=17) compared with Atypical cases with negative EEGs (n=88)

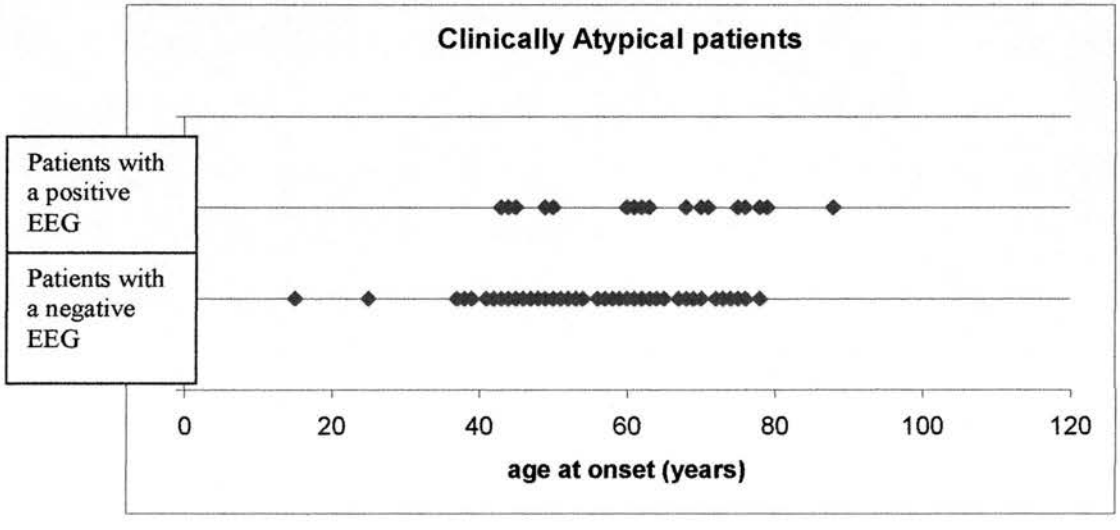


Figure 3.10: Duration of illness in clinically Atypical cases with a) a positive EEG (n=17) and b) a negative EEG (n=88)

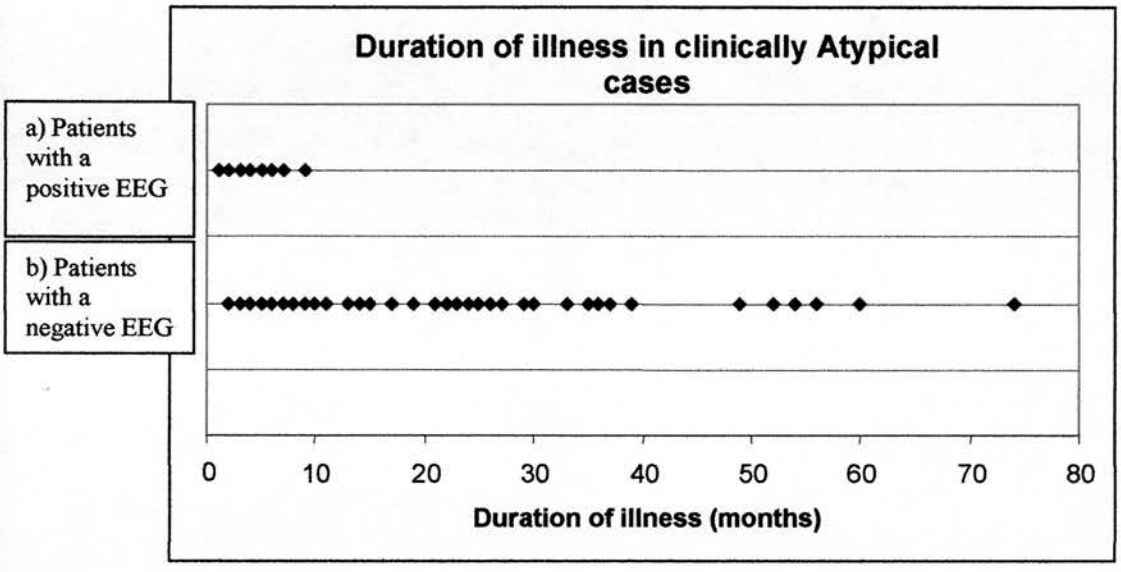
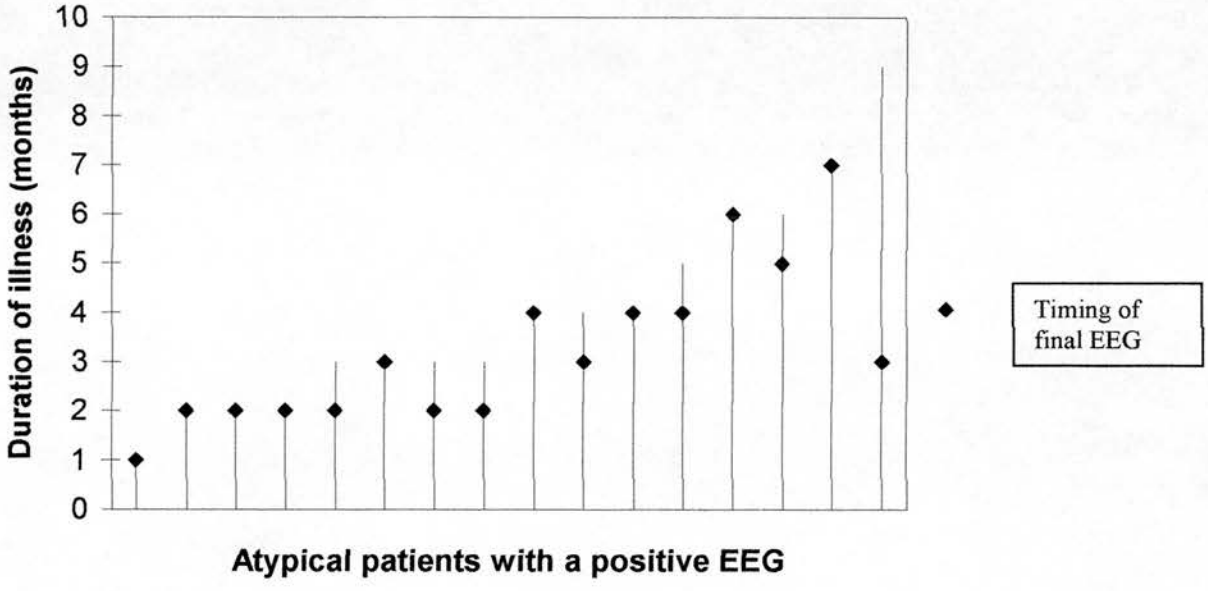
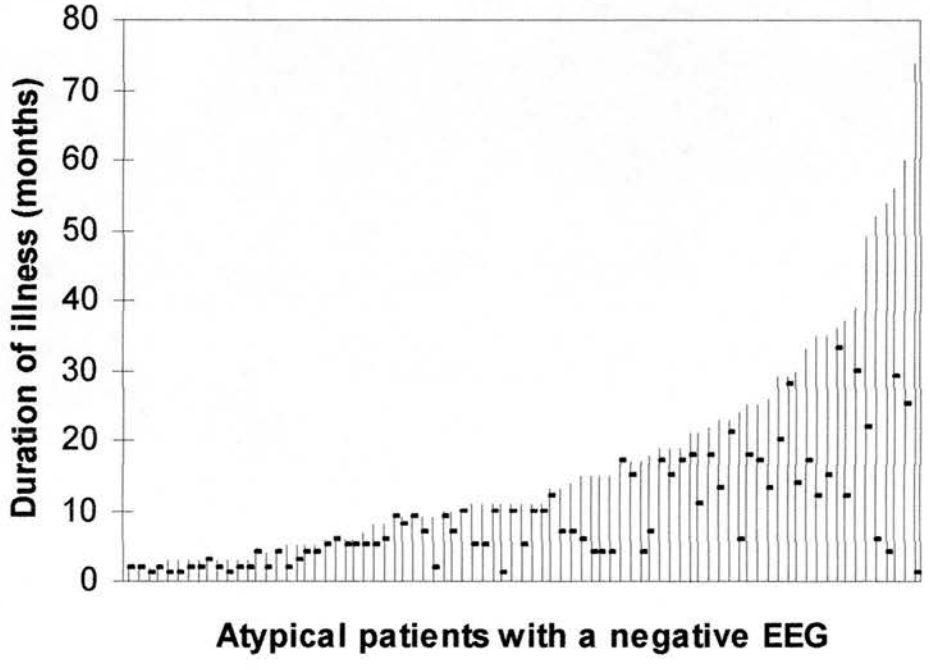


Figure 3.11: Duration of illness (|) and timing of EEG (♦) in a) Atypical sCJD with positive EEG recordings (n=16) and b) Atypical sCJD with negative EEG recordings (where EEG timing known, n=82)

a)



b)



CSF 14-3-3.

This was performed in 42 of the clinically Atypical patients (37%). In seven cases the patient fell into more than one Atypical subgroup (hence 49 results in Table). CSF 14-3-3 showed greatest sensitivity in the cerebellar and visual onset groups (at 83% and 75% respectively) and was less sensitive in the long duration group (at 50%). In sCJD as a whole (i.e. all cases) the sensitivity of this test is approximately 95%[34]. Table 3.17 summarizes the results from each of the subgroups.

Table 3.17: Results of CSF 14-3-3 analysis in Atypical sCJD subgroups

Number tested and % of total tested in brackets

	POSITIVE	NEGATIVE	Unsuitable for analysis
Young (n=17)	12 (71%)	5 (29%)	0
Long duration (n=8)	4 (50%)	4 (50%)	0
Cerebellar onset (n=12)	10 (83%)	2 (17%)	0
Pure visual onset (n=4)	3 (75%)	0	1 (25%)
Other focal onset (n=8)	5 (63%)	2 (25%)	1 (12%)
Core sCJD (n=58)	46 (79%)	4 (7%)	8 (14%)

Due to the fact that 14 % in the Core sCJD were rendered unsuitable for analysis a comparison between positive and negative results in the subgroups and the Core group was not performed.

Cerebral MRI.

MRI sans were available for review at the NCDJSU in 30 cases with Atypical clinical features (some patients had more than one Atypical feature, hence the larger total number of cases in Table 3.18). MRI scans from Atypical cases were compared with scans from the sCJD Core groupwithout Atypical features, matched for scan date within one year (as scan quality varied with the development of MRI as a technique). There was no statistically significant difference (using a chi squared test) between the proportion of patients with high signal in the basal ganglia in each Atypical subgroup and Core sCJD.

Table 3.18: Numbers of patients with basal ganglia high signal on MRI

Total number reviewed in each atypical subgroup in final column (percentages in brackets)

	Basal ganglia high signal present (caudate head and/or putamen)	Basal ganglia high signal absent	TOTAL Number of patients
Young	9 (56%)	7 (44%)	16
Long duration	4 (67%)	2 (33%)	6
Cerebellar onset	8 (80%)	2 (20%)	10
Pure visual onset	0	3 (100%)	3
Other focal onset	2 (22%)	7 (78%)	9
sCJD without Atypical features*	18 (56%)	14 (44%)	32

* where scan dates were matched with the available scans from Atypical cases

The relationship between clinical parameters and high signal in the basal ganglia on brain MRI.

Clincal features, age at disease onset and illness duration were noted for each of the patients where MRI scans were reviewed. High signal in the caudate head and the putamen of the basal ganglia was graded for each individual according to a four point scale: 0=No signal change, 1=normal level of signal change, 2=mildly increased signal, 3=moderately increased signal, 4=strongly increased signal. There was no significant difference between the age at onset or the illness duration in months between those with high signal in the basal ganglia (scoring 2 or more) and those without high signal in the basal ganglia (Wilcoxon rank sum

test). There was no significant positive association between the presence of basal ganglia high signal (grades 2,3 or 4) and any of the following clinical features (recorded for each of the patients): myoclonus, cerebellar signs, involuntary movements (other than myoclonus), extrapyramidal signs, sensory features or pyramidal signs (analysis performed using chi-squared and Fisher's exact tests).

Codon 129 genotype and glycotype.

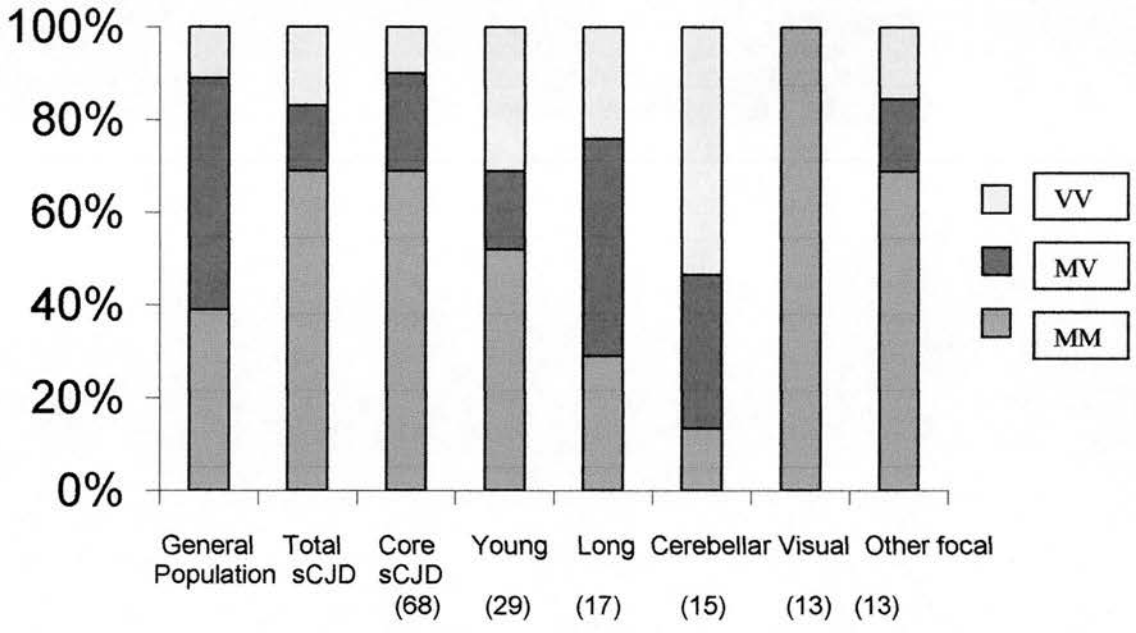
Table 3.19 and Figure 3.12 display the proportions of MM, MV and VV genotypes according to subgroups. Cases with a focal onset and a delayed dementia exhibited approximately the same distribution of genotype as that seen in total sCJD. All of the tested cases that presented with a pure visual onset had an MM genotype. In cerebellar onset cases VV was the most common genotype amongst those tested, in young cases MM was the most common genotype whereas in long duration cases there was an excess of patients with a MV genotype. Glycotype data was not available in all of those with codon 129 genotype data and the available data is summarized in Table 3.19.

Table 3.19: Gentoype and glycotype analysis in tested Atypical cases

	GLYCOTYPE (numbers of patients)			
	Unknown	1	2A	Total
YOUNG				
MM	8	3	4	15 (52%)
MV	4	1	0	5 (17%)
VV	5	2	2	9 (31%)
LONG DURATION				
MM	2	0	3	5 (29%)
MV	4	2	3	8* (47%)
VV	3	1	0	4 (24%)
CEREBELLAR				
MM	1	1	0	2 (13.3%)
MV	2	1	3	5* (33.3%)
VV	1	1	7	8* (53.3%)
VISUAL				
MM	6	7	0	13 (100%)
MV	0	0	0	0
VV	0	0	0	0
FOCAL ONSET				
MM	5	4	0	9 (69%)
MV	1	1*	1*	2* (15.5%)
VV	1	0	1	2 (15.5%)

* One patient exhibited both glycotype 1 and glycotype 2A

Figure 3.12: Distribution of MM, MV and VV genotypes in the general population, sCJD as a whole, Core sCJD and Atypical subgroups
(numbers in brackets indicate numbers within subgroups who were tested)



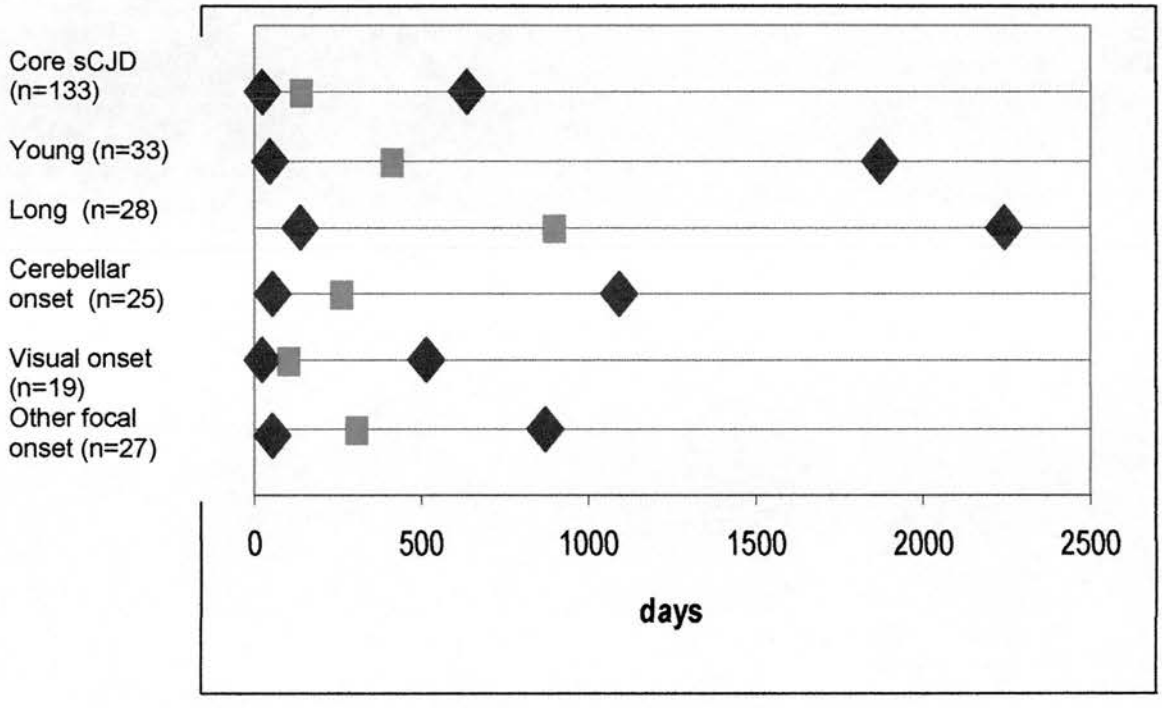
When compared with the distribution of genotype observed in Core sCJD only the long duration and the cerebellar onset cases exhibited a significantly different variation in genotype distribution ($p=0.009$ and $p=<0.001$ respectively, Fisher's exact test). Cerebellar onset cases exhibit more VV and MV genotypes than Core sCJD cases. Long duration cases were more likely to have a MV genotype, with less MM cases. More numbers are needed to understand any potential significance of the MM genotype observed in all of the pure visual onset cases tested (n=13).

Referral to the NCJDSU in Atypical cases

Time from disease onset to notification to the NCJDSU.

The date of notification to the NCJDSU was known for each individual and the number of days from disease onset to notification was calculated for all. This calculation included those who were referred after death but they are considered in more detail in the next section. The range of notification timings in days and the mean for each subgroup (and Core sCJD) is displayed in Figure 3.13. With the exception of cases presenting with a pure visual onset there was a significant delay observed when comparing notification times between the Core group and other subgroups (long cases p=<0.001, cerebellar onset cases p=<0.001, young cases p=<0.001, other focal onset cases p=<0.001, Wilcoxon ransksum test). Pure visual onset cases were more likely to be referred earlier in the disease when compared with the Core group (p=0.046, Wilcoxon ranksum test). Fifteen of the 19 pure visual onset cases (79%) were referred initially to an ophthalmologist. Two cases with a pure visual onset of disease had cataract extractions performed after symptom onset and before the diagnosis of sCJD was made.

Figure 3.13: Time from disease onset to NCJDSU notification in Core sCJD and Atypical sCJD
(range of notification timing (minimum and maximum) indicated by the diamond, mean time to notification indicated by the square)



Applying the diagnostic criteria to Atypical cases.

Patients living for greater than two years did not meet the criteria for a case of sCJD (see Table 1.10) because illness duration of greater than two years was an exclusion criteria*. Eleven (33%) young cases did not meet the criteria for a case of sCJD. In eight this was because the disease duration exceeded two years, in one because the patient was not considered to have a "rapidly progressive" dementia, in one because of a lack of neurological signs and in one because of a lack of clinical information. In young, long duration and other focal onset cases there was a higher proportion who

* If the EEG was negative, as it was in all of these cases

did not meet the clinical criteria for a case when compared with Core sCJD (33%, 100% and 26% respectively versus 7% for Core sCJD with p=<0.001, p=<0.001 and p=0.005 respectively (Fisher's exact test). Pure visual onset cases were most likely to meet the case definition with over 95% being classified as Possible or Probable sCJD (at a comparable level to that seen in Core sCJD). The proportion of cases meeting the definitions for Definite, Probable and Possible sCJD are summarized in Figure 3.14.

In light of the finding that some of the focal onset sCJD cases may present with isolated sensory or psychiatric features the case definition for vCJD (see Appendix 1) was applied to the cases in whom these features were described at onset (n=16). Five of these patients met the criteria for a Possible case of vCJD. None met the criteria for a Probable case of vCJD. In the five "Possible vCJD" cases the diagnosis of sCJD was considered more likely in four and vCJD considered more likely in one case. Three of these cases were younger than 50 years of age.

Table 20 summarizes the significant differences observed in Atypical subgroups when compared with Core sCJD.

Figure 3.14: Final classifications in Core sCJD and sCJD subgroups

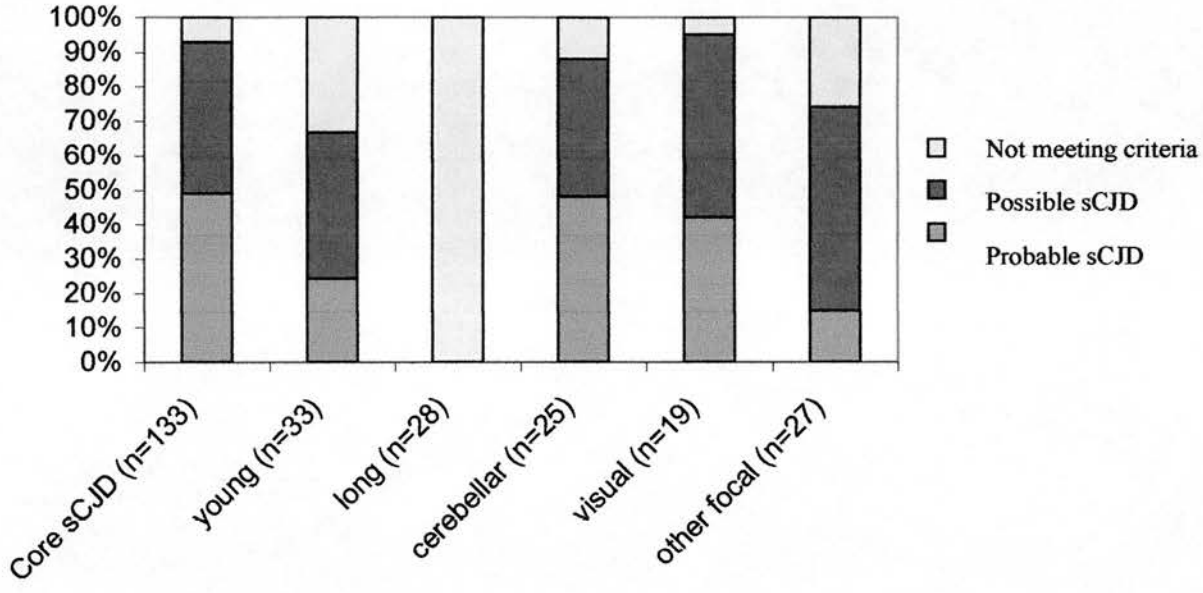


Table 3.20a: Features associated with Atypical subgroups (young, long duration and pure cerebellar onset) when compared with Core sCJD

Atypical Subgroup	Feature significantly associated with subgroup when compare to Core sCJD
Young cases	• Less unsteadiness/ataxia at onset • More personality/behaviour change at onset • More psychiatric symptoms & involuntary movements (other than myoclonus) throughout the illness • Less cerebellar or extrapyramidal features throughout the illness • Later notification to the NCJDSU • Less likely to have a positive EEG • Less likely to meet the criteria for a Possible or Probable case in life
Long duration cases	• Younger age • Personality/behavioural change and depression more common at disease onset • Unsteadiness/ataxia less common at onset • More psychiatric features throughout the illness • Less extrapyramidal or cerebellar features throughout the illness • Less likely to have a positive EEG • More MV and VV genotype at codon 129 and less MM • Later notification to the NCJDSU • Not meeting the criteria for a Possible or Probable case
Pure cerebellar onset cases	• Longer illness duration • Younger age at onset but only one younger than 50 years of age • More visual disturbance, sensory symptoms and psychiatric symptoms throughout the illness • Less likely to have a positive EEG • Less MM and more MV and VV genotype at codon 129 • Later notification to the NCJDSU

Table 3.20b : Features associated with Atypical subgroups (visual and other focal onset) when compared with Core sCJD

Atypical Subgroup	Feature significantly associated with subgroup when compared with Core sCJD
Pure visual onset	• Shorter disease duration • Less extrapyramidal and cerebellar signs throughout the illness • Early notification to the NCJDSU • All tested cases had an MM genotype
Other focal onset cases	• Younger age • Longer illness duration • More sensory and psychiatric symptoms and involuntary movements (other than myoclonus) throughout the illness • Less extrapyramidal and cerebellar signs throughout the illness • Later referral to the NCJDSU • Less likely to meet the criteria for a Possible or Probable case

Summary of findings in Atypical cases

- Approximately one quarter of all patients with pathologically proven sCJD possess one or more Atypical features according to the criteria used in this study.
- Young cases are associated with symptoms of personality or behavioural change at onset and more psychiatric symptoms and involuntary movements during the illness that that observed in Core sCJD.
- Long duration cases are more likely to present with depression or personality/behavioural change. The majority of long duration cases exhibit a genuinely slower disease progression (only two were reported as losing the ability to walk within one year).
- Ataxia is less commonly observed at onset in the young or those who live for more than two years.
- Apart from in cases presenting with a pure cerebellar syndrome, extrapyramidal signs and cerebellar signs are less commonly observed in Atypical cases.
- Pure cerebellar onset cases complain of more sensory symptoms and visual disturbance than Core sCJD cases. Psychiatric symptoms are also more common in this group. There are more men than women presenting in this way, at a ratio of 2.1 to 1.0, although numbers are small.
- Cases presenting with pure visual symptoms live for a shorter period and are notified earlier to the NCJDSU than Core sCJD. In our series all tested pure visual onset cases had a MM genotype at codon 129 of the prion protein gene.
- Sensory and psychiatric symptoms and involuntary movements (thoughout the course of the illness) are associated with cases presenting with focal symptoms (other than cerebellar or visual problems).

- Patients with a focal onset tend to be younger and live for longer than those in the Core sCJD group.
- Amongst Atypical cases a positive EEG is associated with an older age at disease onset, a shorter disease duration and an MM genotype. With the exception of pure visual onset cases, a positive EEG is less likely to be observed in clinically Atypical cases.
- There are no significant associations between patient age, disease duration, Atypical subgroup, specified clinical features and the presence of basal ganglia high signal on cerebral MRI in a group of 62 sCJD cases.
- With the exception of pure visual onset cases, there is a significant delay observed in the notification of Atypical cases to the NCJDSU.
- Occasionally, cases with a pure visual onset of disease may undergo needless ocular surgery

Cases referred by neuropathologists after autopsy

Ninety one (19%) out of 485 pathologically proven cases of sCJD were not referred to the NCJDSU whilst the patient was alive but were notified after a postmortem examination had confirmed the diagnosis of sCJD.

These cases comprised of those in whom the diagnosis of CJD was not suspected at all and cases in whom the diagnosis of CJD had been raised as a possibility. Twenty six cases out of the 91 (29%) were not suspected to have CJD in life. In 65 unreferred cases (71%) CJD was considered to a varying extent (ranging from one of a number of suggested diagnoses to a clear clinical decision that sCJD was the most likely diagnosis) but despite this a referral to the NCJDSU was not made. The age distribution of all cases referred after autopsy (suspected and unsuspected) is shown in Figure 3.16. Those referred after autopsy were older than the cases of sCJD in this cohort referred before autopsy (n=393) (Wilcoxon ranksum test, p=0.005). The distribution of illness duration in those referred before and after autopsy is summarized in Figure 3.17. Cases referred after autopsy tended to be of longer duration than those referred in life (p=0.044, Wilcoxon ranksum test).

Unsuspected cases of sCJD

Twenty six (5%) of total pathologically proven sCJD cases were not suspected to have CJD whilst they were alive. The mean age at onset in this group was 70 years (median 68 years, range 44 to 94 years). Mean duration of illness in this group was 15 months (median 7 months, range 2-74 months). Thirteen cases were men, thirteen were women. In seven cases no alternative diagnosis was

proposed and in five cases Alzheimer's disease was cited as either the most likely diagnosis or as one of two potential diagnoses. A summary of the proposed alternative diagnoses in these cases is given in Table 3.21. A summary of the presenting features amongst unsuspected cases is found in Table 3.22. Presenting features were comparable to those seen in sCJD (see Table 3.1) where the diagnosis had been suspected before death.

Table 3.21: Alternative diagnoses that were considered in unsuspected autopsy proven sCJD cases

Final clinical diagnosis in unsuspected group with neuropathologically proven sCJD	Number of patients (n=26)
No diagnosis given	7
Alzheimer's disease	3
Cerebrovascular disease	3
Alzheimer'sdisease/Pick'sdisease	1
Alzheimer's disease/cerebrovascular disease	1
Pick's disease	1
Paraneoplastic syndrome	3
Squamous cell lung cancer	1
Motor neurone disease	1
Cerebral infarct & motor neurone disease	1
Alcohol excess contributory	2
Ischaemic diabetes mellitus-related cerebellar degeneration	1
Progressive supranuclear palsy	1
TOTAL	26

Table 3.22: Presenting symptoms in the unsuspected group

(more than one symptom may be present at onset)

Presenting symptom	Unsuspected sCJD (n=26)
Memory loss, confusion, forgetfulness or disorientation	10
Gait unsteadiness	8
Weakness of limb(s)	3
Speech difficulties	3
Dizziness/vertigo	2
Anxiety	2
Sensory disturbance	2
Visual disturbance	1
Depression	1
Paranoia	1
Lethargy	1
Social withdrawal	1

Clinically "typical" unsuspected cases.

In five (19%) of these 26 unsuspected cases the clinical course was clearly documented as a rapidly progressive dementia with myoclonus and a duration of illness of less than six months. Only one of these patients with an apparently typical course had been seen by a neurologist. Seven (27%) other unsuspected cases had a rapidly progressive dementia with a duration of less than six months but the presence of specific neurological signs was uncertain. Three of these seven patients had been assessed by a neurologist. In total 12 (46%) of the clinically unsuspected group had an illness duration of less than six months, with four having been assessed by a neurologist. A summary of the number of cases referred after autopsy that were assessed by a neurologist can be found in Figure 3.19.

Atypical features in the unsuspected group.

When criteria for an Atypical case are applied to the unsuspected cases, 10 (38%) possessed Atypical features. These Atypical features were a long duration of illness (>two years) in six, a young age at onset (<50 years) in two, presentation with a pure cerebellar syndrome in one and a focal onset (other than with cerebellar or visual symptoms) in three. Two patients were both young and had a long duration of illness. Both were women (aged 44 and 48 years with disease durations of 60 months and 37 months respectively) and the clinical diagnosis in life was that of Alzheimer's disease. The two patients with the longest duration of illness in the total sCJD group in this study (n=485) were unsuspected cases (with durations of illness of 60 and 74 months).

In addition to defined Atypical features the following characteristics were noted in six other patients, which caused diagnostic confusion:

1 An Electromyelogram (EMG) reported as showing "large motor unit potentials in all muscles sampled with fasciculation potentials....this must be motor neurone disease" in one case.

2 A duration of illness of 23 months in one patient associated with a slower than expected progression of dementia and physical impairment.

3 The coexistence of sCJD and Alzheimer's disease at postmortem (clinically at least three years of cognitive decline followed by a rapid deterioration lasting three months) in one case.

4 A diagnosis six months prior to disease onset of an inoperable squamous cell lung cancer.

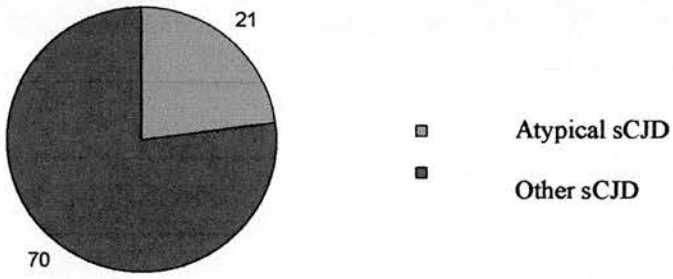
5 Alcoholism (in two patients)

When compared with Core sCJD long duration cases were found to be more likely to be referred after autopsy ($p=0.05$, Fisher's exact test). Although there were variations in the number referred pre and post autopsy between Atypical subgroups and Core sCJD (see Figure 3.18) these did not reach statistical significance. Twelve (46%) of the unsuspected cases were assessed by a neurologist. One other case was discussed over the telephone with a neurologist but was not seen.

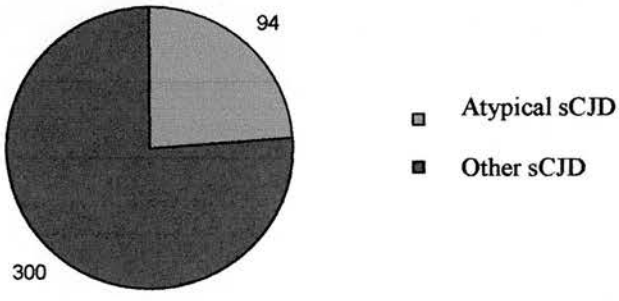
Figure 3.15 displays the proportion of cases with Atypical features amongst those referred both before and after autopsy. As the graphs display the proportion of Atypical cases is very similar in both groups.

Figure 3.15: Proportion of cases with Atypical features in those referred before and those referred after autopsy

a: Proportion of Atypical cases amongst sCJD referred after autopsy (n=91)



b: Proportion of Atypical cases amongst sCJD referred before autopsy (n=394)



Applying the case definition to unsuspected cases.

Classifying the patients in retrospect according to the case definition for sporadic CJD was problematic, as many of the clinical features commonly observed in CJD had not been documented (as either present or absent). However, none of the patients met the criteria for a Probable case (due to the lack of supportive investigations being performed). Thirteen met the criteria for a Possible case. The remaining 13 did not meet the definition for a case of sCJD due either to long duration (in six cases), documented lack of physical signs (in five cases) or an absence of reliable clinical data (in two)

The importance of accurate premortem diagnosis of CJD is again highlighted by the occurrence, in one of the unsuspected cases, of corneal donation after death for transplantation into two other individuals (a reported method of onward transmission of the disease producing agent).

Clinically suspected but unreferred cases

Sixty five (71%) of the 91 unreferred cases were not notified to the NCJDSU in life despite the diagnosis of CJD being raised. In 30 (46%) of these suspected cases review of the case-notes revealed that CJD was considered the most likely clinical diagnosis. In 25 (38%) the diagnosis of CJD was mentioned at least once but often in the context of other potential diagnoses and was not highlighted as the most likely diagnosis. In ten cases there was not enough clinical information to be sure of the degree of diagnostic certainty. Forty four of these suspected cases (68%) underwent assessment by a neurologist. The involvement of neurologists in these unreferred cases is summarized in Figure 3.19. The difference between the proportion of unsuspected

and suspected cases seen by neurologists (46% and 68%) is not significant when Fisher's exact test is applied (p=0.09). The place of residence of each unsuspected case was plotted on a map of the United Kingdom (see Figure 3.21) with the aim of identifying if the unreferred cases were originating from the same areas. Unreferred cases show a wide distribution throughout the United Kingdom with a higher number of cases in some of the larger cities (as would be expected with a greater population density).

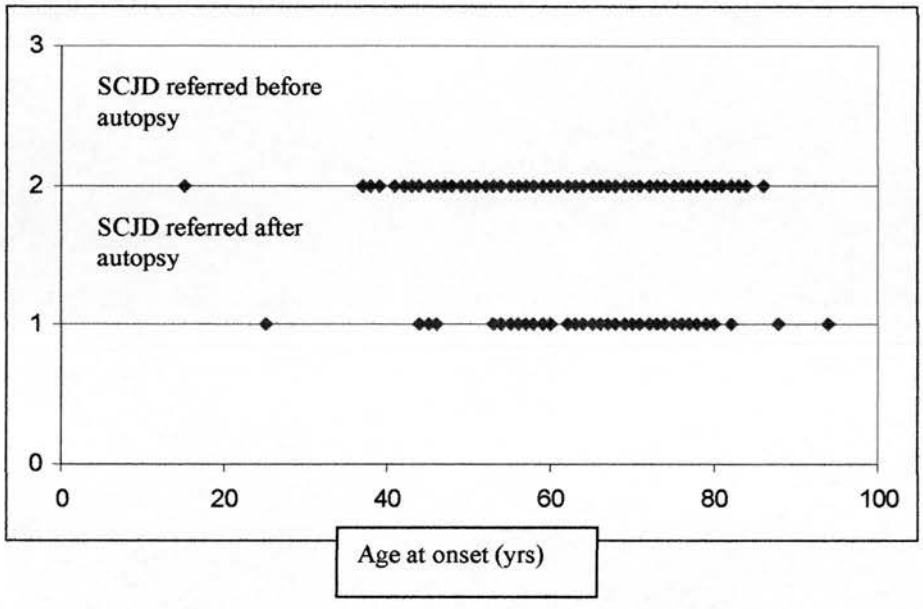
Investigations in cases referred only after autopsy

Of the 91 cases referred to the NCJDSU after autopsy, 57 (63%) were documented as having had an EEG recording. Of these, seven (12%) showed an appearance considered positive for sCJD upon review by the NCJDSU. All of these seven were thought to have sCJD by the clinical team involved but the NCJDSU was only contacted in one case. In this case CSF was tested for 14-3-3 but the result was negative and the patient was not referred on for a clinical opinion. Only three cases had CSF examined for 14-3-3 and in all three it was negative. Cases with positive CSF 14-3-3 would become classified as formal "referrals" whilst alive as there is close communication between the CSF laboratory staff and the clinicians at the NCJDSU. It is less clear how many of these patients underwent brain MR imaging and the scans were infrequently available for review by NCJDSU staff.

Distribution by year of all cases referred after autopsy

There was a variation year on year of the number of cases not referred in life to the NCJDSU. Figure 3.20 demonstrates the number of pathologically proven cases of sCJD identified per year with the proportion which were only notified after autopsy. It demonstrates that the overall number of cases referred to the NCDJSU until the end of 2002 is showing an increasing trend which is not reflected in the number of cases referred after autopsy. Figure 3.22 breaks down these unreferred cases into those who were suspected and those who were unsuspected, by year of notification. In 1997 both the greatest number of overall post-mortem examinations and the greatest number of cases referred after autopsy occurred. There has been a decline in autopsy rates for CJD recently, as Figure 3.23 demonstrates.

Figure 3.16: Age at onset of cases referred before autopsy (n=393) and cases referred after autopsy



Each mark represents one patient

Figure 3.17: Duration of illness in sCJD (n=391) referred before autopsy and sCJD referred after autopsy

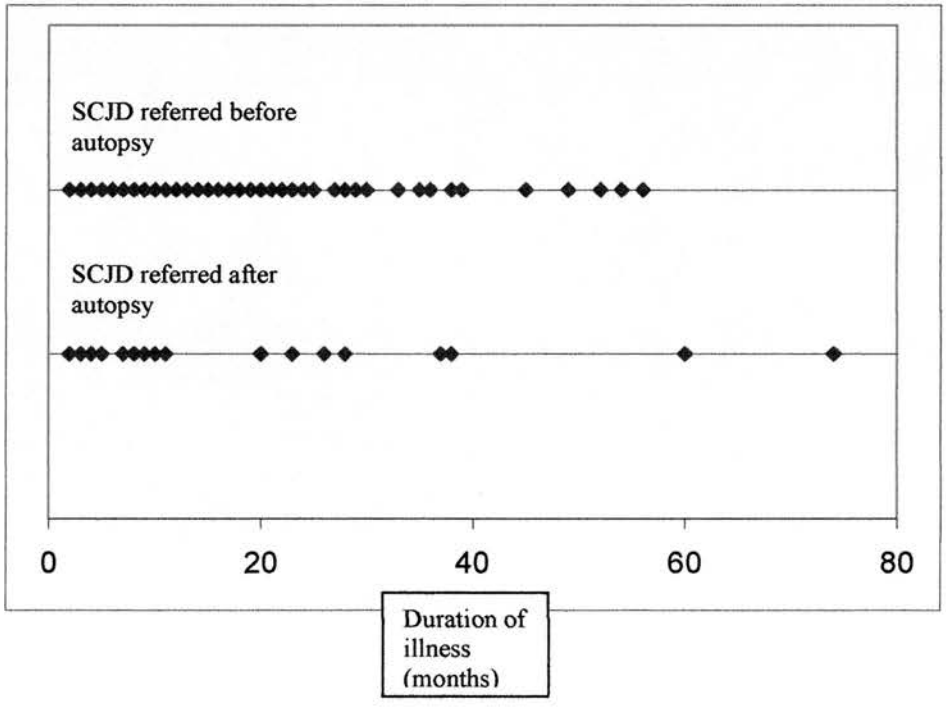


Figure 3.18: Percentage of cases in atypical subgroups referred after postmortem compared with Core sCJD and total sCJD

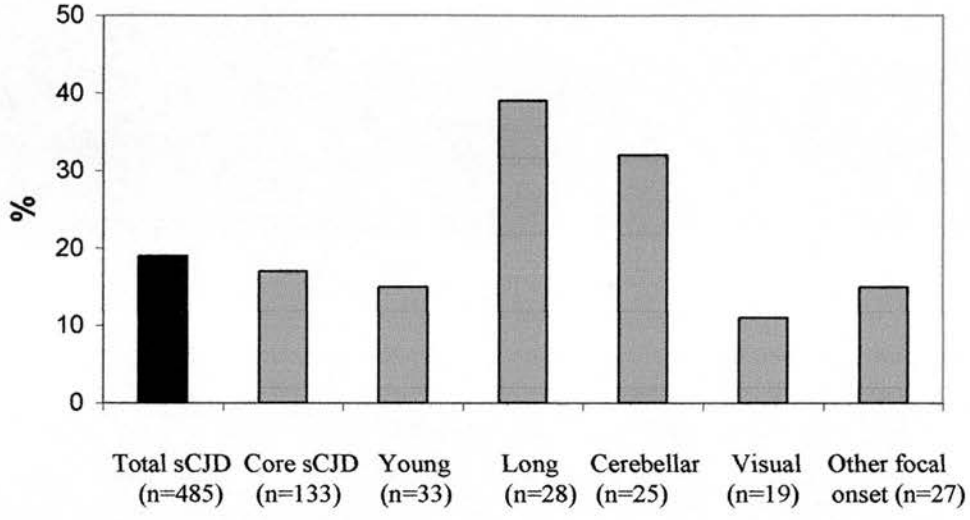


Figure 3.19: Number of cases referred after autopsy that were seen by a neurologist (1990-2002).

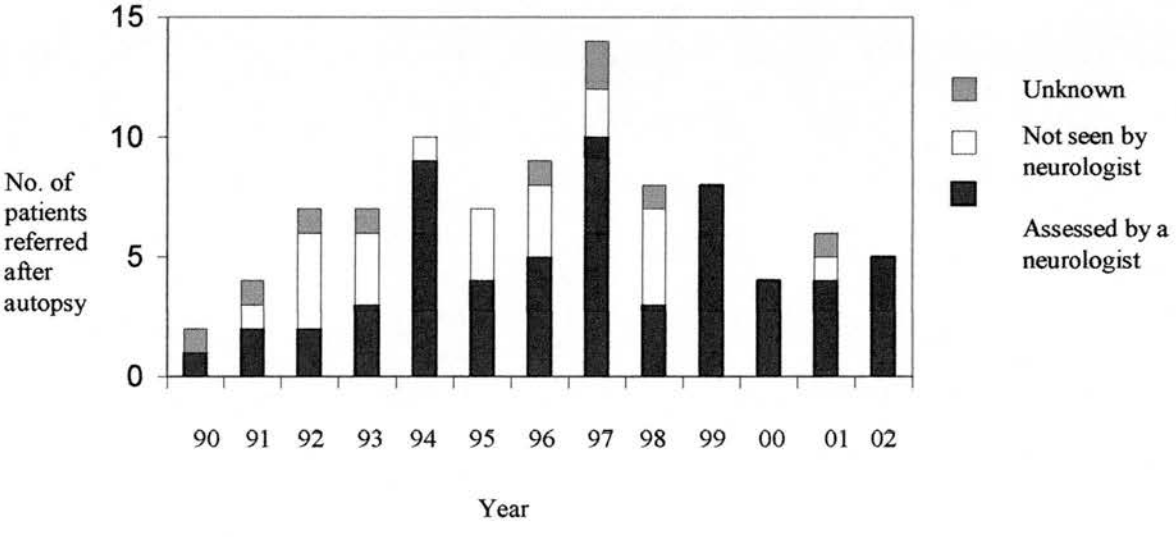


Figure 3.20: Number of cases referred after autopsy over time compared with total referral numbers over time

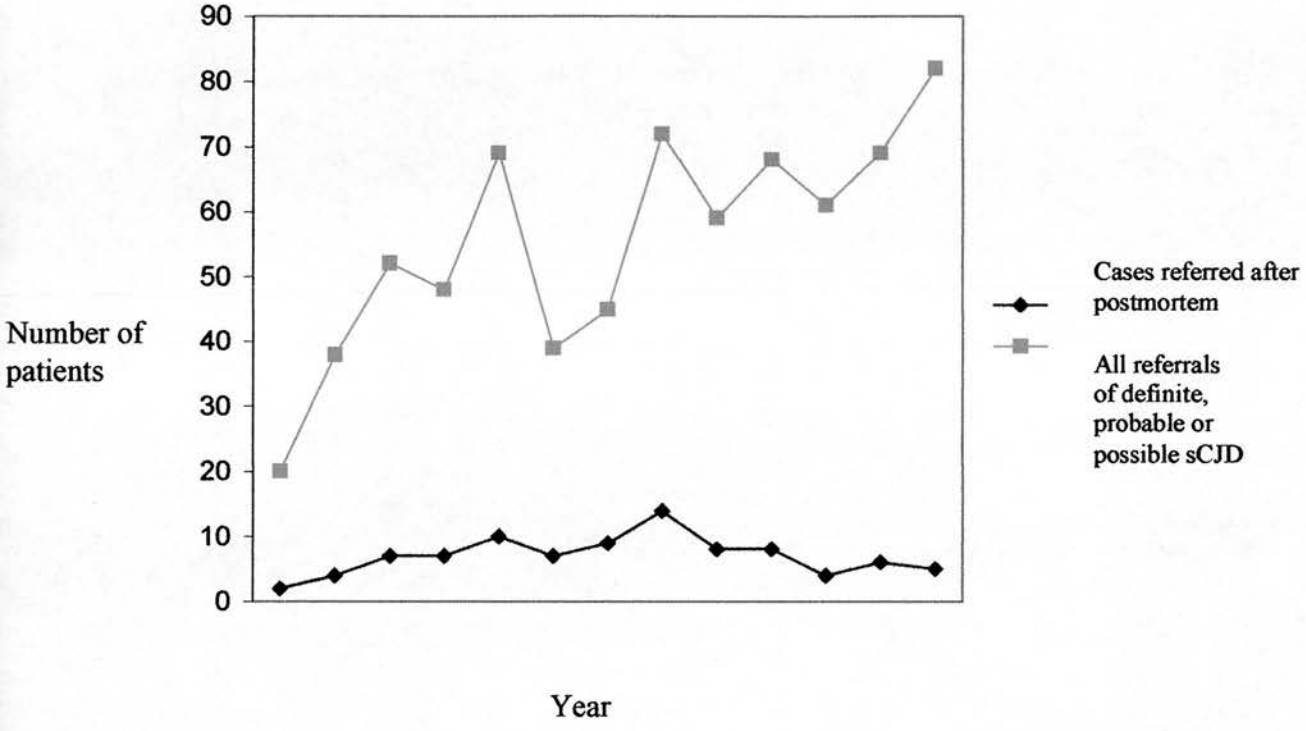


Figure 3.21: Map showing places of residence of cases of sCJD only notified after autopsy (n=91)

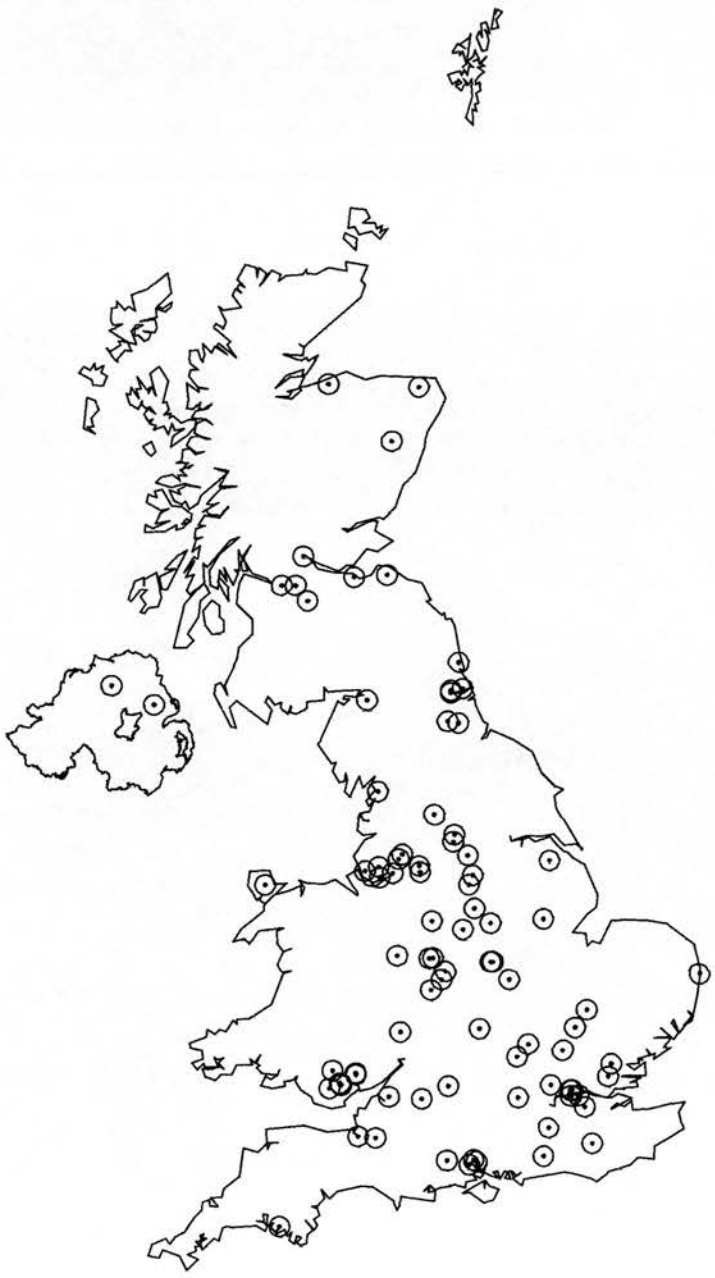


Figure 3.22: Number of cases notified after autopsy that were suspected and unsuspected 1990-2002

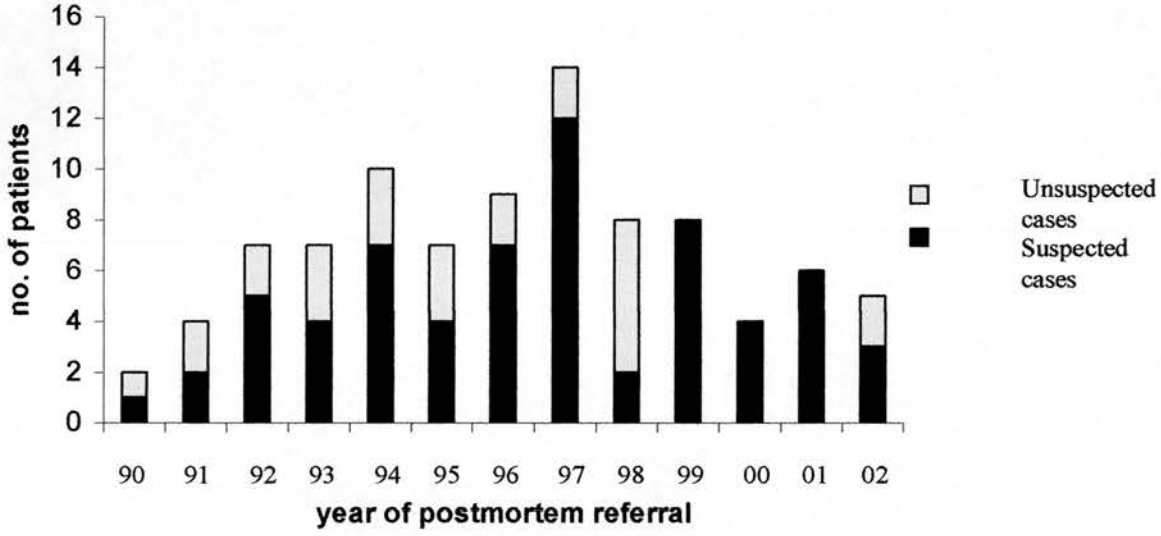
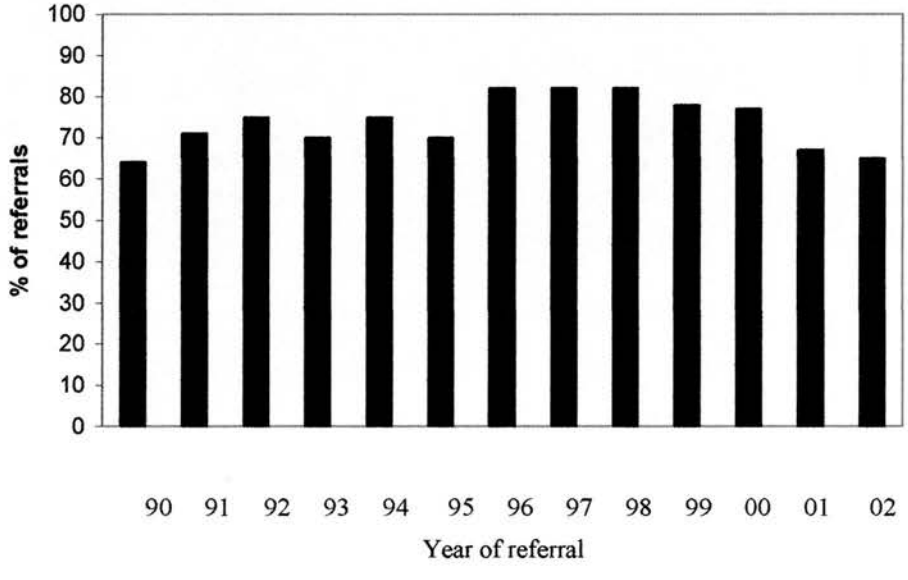


Figure 3.23: Percentage of referrals of suspected CJD coming to autopsy in the UK, 1990-2002 (source NCJDSU data)



Summary of findings in cases referred to the NCJDSU after autopsy

- 19% of all pathologically proven sCJD cases were only notified to the NCJDSU after autopsy.
- In just under one third of these cases the diagnosis of CJD was not suspected in life.
- Cases referred after autopsy were significantly older than those referred before autopsy.
- Disease duration was significantly longer in the group referred after autopsy compared with sCJD cases referred before autopsy.
- 38% of unsuspected cases showed Atypical features according to our definition
- Just less than one half of the unsuspected cases appeared to have a typical clinical course that went unrecognised.
- Neurologists were involved in 46% of unsuspected cases and 68% of suspected cases that were not notified in life.
- There were no clear geographical areas that corresponded with cases unreferred in life, although numbers were small.
- There are not an increasing number of cases being referred after autopsy, which may in part reflect the decreasing postmortem rates seen in the UK.

Possible sCJD

Between 1990 and the end of 2002, 59 referrals have been made to the NCJDSU of patients who were finally classified as Possible sCJD. The diagnosis in these patients remains uncertain and they are not included in the national statistics for CJD cases.

According to the case definition for sCJD (see Table 1.10) for a patient to be a Possible case they must possess a rapidly progressive dementia plus two of the following: extrapyramidal/ pyramidal signs; akinetic mutism; cerebellar/visual problems or myoclonus with a duration of illness of less than two years. To be classified as a Probable case these criteria need to be met along with a positive supportive investigation (CSF 14-3-3 or EEG).

Distribution of Possible cases over time

There has been a general increase over time in the number of Definite, Probable and Possible sCJD cases referred to the NCJDSU (apart from a dip in referral numbers in 1995 and 1996) (see Figures 3.24a and 3.24b). The overall proportion of Probable cases has risen over time which may reflect the decreasing trend for autopsies to be performed (see Figure 3.23). The proportion of Possible cases has fluctuated over the 12 years of surveillance (Figure 3.24).

Figure 3.24a: Numbers of Definite, Probable and Possible sCJD by year of referral

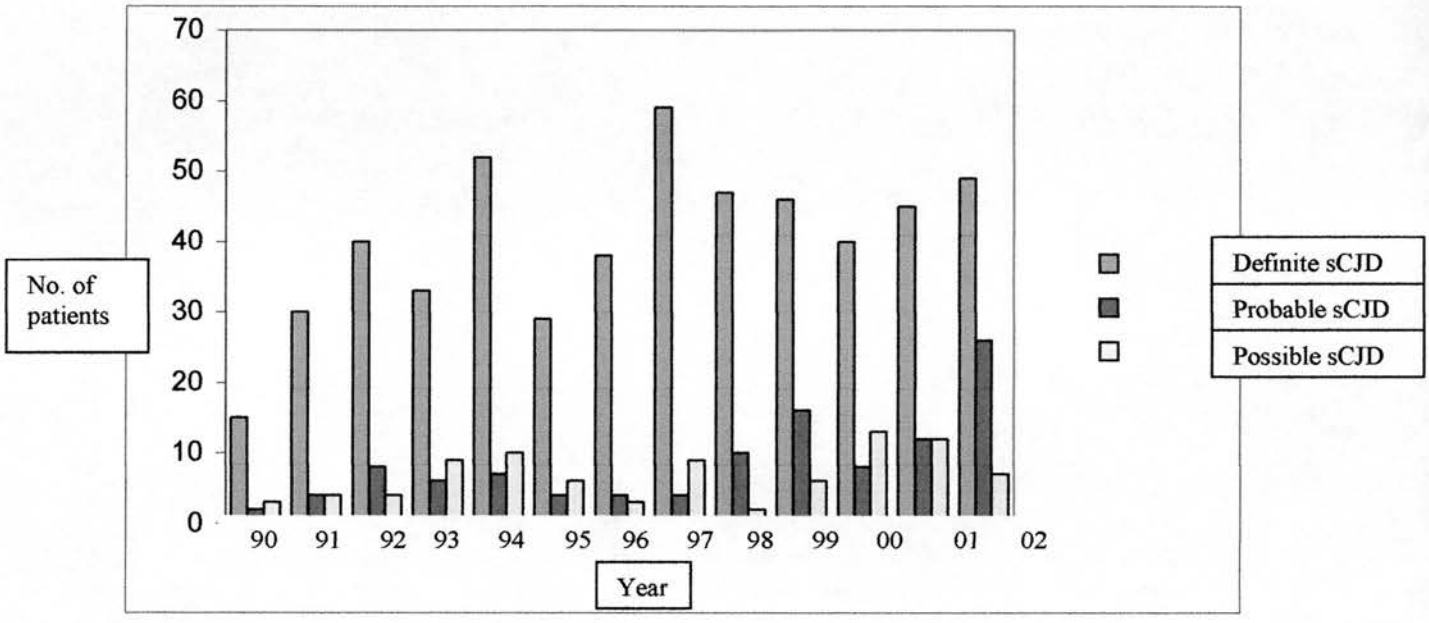


Figure 3.24b: Overall number of Definite, Probable and Possible sCJD referrals 1990-2002

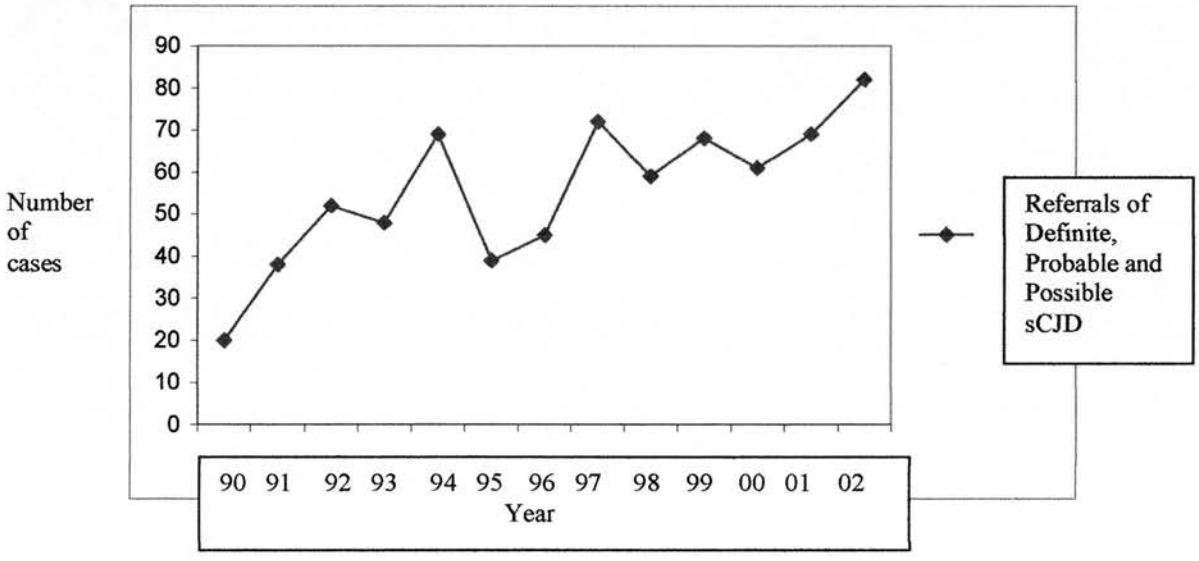
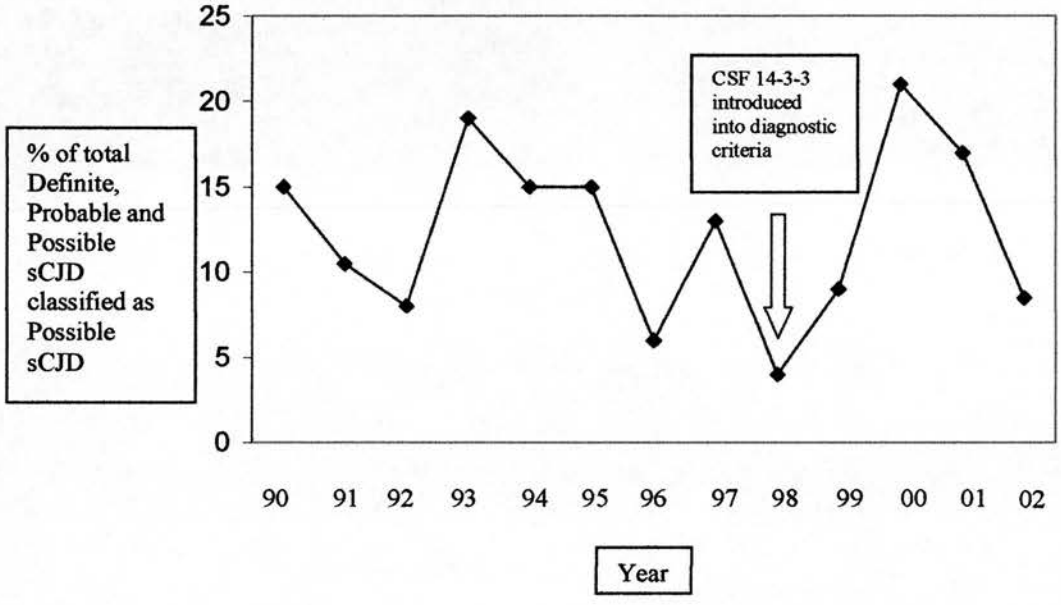


Figure 3.25: Percentage of total Definite, Probable and Possible sCJD finally classified as Possible sCJD by year of referral



Clinical features in Possible cases

33 (56%) of the Possible cases were women. The mean age at onset in this group was 73 years (median 68 years, range 37-89 years). The mean duration of illness in the Possible cases was 5 months (median 4 months, range 2-13 months). Sixteen (31%) had a disease duration of three months or less associated with myoclonus. In these cases the clinical picture strongly resembled that seen in sCJD but all lacked a positive supportive investigation.

Investigations in Possible cases

A positive investigation is required for a Possible case to be classified as Probable. The absence of a positive investigation may either occur because the investigation has not been performed or because the investigation was negative. Taking sCJD as a whole, CSF 14-3-3 is negative in about five per cent of total sCJD. The EEG needs often to be repeated for a positive result to be obtained and a negative result may indicate that the test has not been employed to its best advantage.

Six (10%) of the 59 patients with a classification of Possible CJD had CSF 14-3-3 analysis performed. Three of these were negative and three were bloodstained (rendering them unsuitable for analysis). The reasons why CSF 14-3-3 was not performed in the remaining 53 patients are summarized below:

	n
Patient's illness predated the availability of the test	33
Lumbar puncture performed but 14-3-3 not requested	5
Lumbar puncture not considered	5

Family did not wish for the test to be performed	3
Patient considered too unwell	1
Information not clear	6

EEG was performed in 51 out of 59 (86%) and none showed the characteristic periodic sharp wave complexes. In 27 (46%) of these only one EEG was performed. The timing of the EEGs (where known) in terms of proportion of illness passed is expressed in Figure 3.26. This shows that only 13 patients with a diagnosis of Possible sCJD (22%) had an EEG recording in the final month of their illness. The number of EEG recordings per patient is shown in Figure 3.27. Eighty two per cent had one or two EEG recordings only.

Nine patients with a diagnosis of Possible sCJD (15%) had an MRI scan which was available for review by an experienced neuroradiologist at the NCJDSU. Three showed definite high signal in the basal ganglia and one showed basal ganglia high signal "probably consistent with sCJD but not typical". The remaining five scans showed vascular disease in three, high signal in the right frontal area of unknown significance in one and a normal examination in one.

The codon 129 genotype was only known in eight cases (14%). Five were MM, two were MV and one was VV. In 27 cases (48%) a referral was made and the patient was assessed whilst alive by a NCJDSU doctor. In 24 cases (41%) the patient was not referred to the NCJDSU until after death. Five patients (8%) were referred but not seen before death and in three cases it is unsure when a patient was referred to the NCJDSU (but they were not seen in life).

Figure 3.26: Timing of final EEG recording (◆) as a proportion of the total illness passed in Possible sCJD (all these EEGs were negative)
(100% refers to EEG being performed in final month of illness)

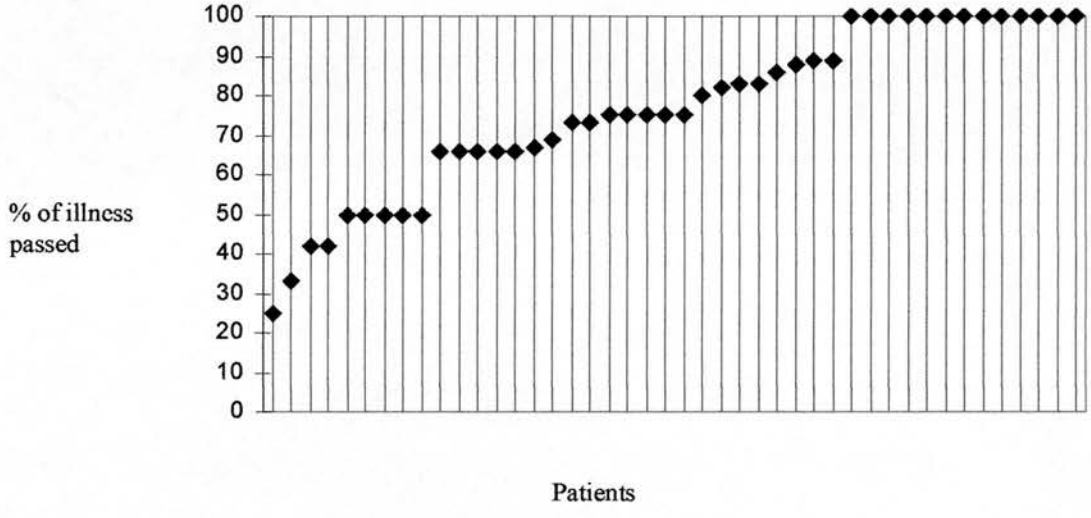
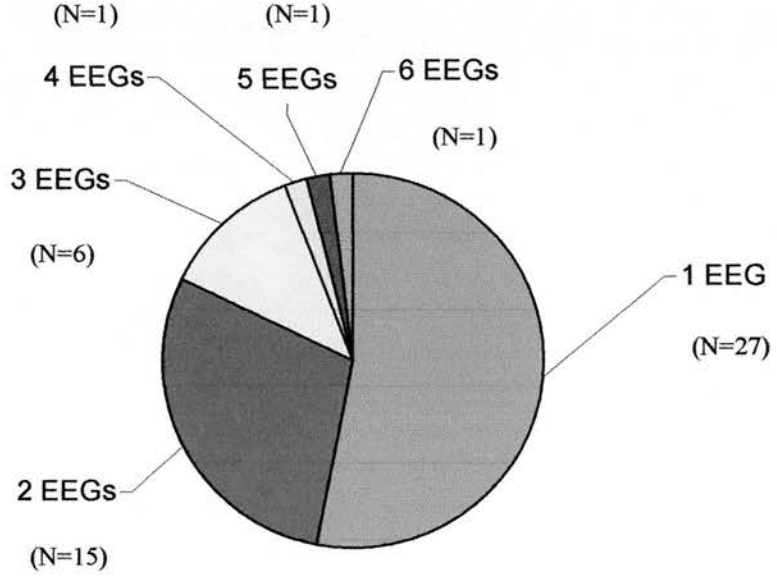


Figure 3.27: Number of EEGs performed per patient in Possible sCJD
(51 patients)



Summary of findings in Possible cases

- 59 cases of suspected sCJD referred to the NCJDSU from 1990-2002 have remained as Possible sCJD only. This equates to an average of 4.9 cases per year
- 16 (23%) of these cases had a clinical course that was strongly suggestive of sCJD (i.e. duration of illness three months or less with myoclonus)
- Many cases were not fully investigated
- The NCJDSU was involved in just over half of the cases whilst the patient was alive.
- If the MRI scan were to be included in the diagnostic criteria with the same weighting as the EEG or CSF 14-3-3 it would only allow three (out of 59) further patients to be reclassified as Probable, but many scans were not available for review.
- Following on from the introduction of CSF 14-3-3 the number of cases classified as Possible has not decreased. Reasons for this shall be discussed.

Not CJD

Alternative diagnoses

Approximately eleven per cent of referrals made to the NCJDSU with suspected CJD have an alternative diagnosis proven at autopsy *. A summary of the alternative diagnoses in the 182 cases referred to the NCJDSU (1990-2002) with initially suspected CJD (who subsequently had an autopsy confirming an alternative diagnosis) is found in Table 3.23. The three most common alternative diagnoses are Alzheimer's disease (AD) (37% of pathologically proven not CJD cases), Lewy body dementia (LBD)(13%) and cerebrovascular disease(CVD)/ multi infarct dementia (9%).

Clinically selected pathologically proven non sCJD

A previously undiagnosed case of sCJD.

A case file review of the clinical features and investigation results in the 45 non cases referred with suspected sCJD who were assessed by a NCJDSU doctor whilst alive was performed. One of the patients displayed many of the features considered typical for sCJD. He was an 84 year old man who developed a rapidly progressive dementia associated with ataxia and myoclonus. After a period of just over two months from the symptom onset he was akinetic and mute. Death ensued by three months. An EEG recording taken in the final month of the illness showed an appearance considered positive or "typical" for sCJD (reviewed blinded to diagnosis

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* Approximately 1650 cases referred to the NCJDSU by the end of 2002 of which 182 had other diagnoses proven at autopsy

at the NCJDSU according to the criteria outlined in Appendix 2). He died prior to the advent of CSF 14-3-3 as a diagnostic test but did meet the criteria for a Probable case of sCJD. The original pathological diagnosis was Alzheimer's disease with angiopathy and infarcts.

In light of the clinical features, which convincingly supported a diagnosis of sCJD despite neuropathology to the contrary, a review of the autopsy findings was requested. Further histological examination was carried out using Paraffin Embedding Tissue (PET) blotting** which detected PrP deposition in the temporal lobes. This technique is more sensitive than conventional immunocytochemsitry as it can detect smaller amounts of PrP^{Sc}. This was considered to be an unusual finding indicative of early Prion disease (personal communication, Professor James Ironside). In view of the clinical features it was taken to represent a dual pathology of Alzheimer's disease and sCJD.

Following on from this the clinical features of the remaining 44 clinically selected non cases were reviewed to see if neuropathological review would be warranted in further cases. Two male patients died with an autopsy diagnosis of Alzheimer's disease (in one case with coexisting cerebrovascular disease) where myoclonus was clearly documented and the duration of illness was less than six months. In both cases there had been a rapidly progressive dementia and in one case the patient had become akinetic and mute after three months. EEG recordings were not considered typical for sCJD, CSF 14-3-3 had not been performed and they had both met the clinical criteria for Possible sCJD. In these cases, however, an extensive review of the

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** This technique differs from routine immunocytochemistry in that the paraffin tissue is embedded onto a nitrocellulose membrane. This can then be treated with lower concentration of Proteinase K than is

neuropathology with further immunocytochemistry and PET blotting failed to demonstrate any evidence of sCJD.

Alternative diagnoses in clinically selected non cases.

In the 44 clinically selected non cases with suspect sCJD the most common alternative diagnosis was Alzheimer's disease in 20 (45%)***. Lewy Body Dementia was proven in five (11%) and cerebrovascular disease in four (9%). These cases represented those where the patient had been assessed in life by a NCJDSU neurologist. Neoplastic or paraneoplastic disease was the underlying diagnosis in six cases (14%). Despite an autopsy the diagnosis remained unknown in three cases. These findings are summarized in Table 3.24. The most common reasons for referral to the NCJDSU include a "rapid deterioration" of cognitive function (cited in 35 patients (80%)) and the presence of a dementia with added features (especially myoclonus) (see Table 3.25).

Illness duration in clinically selected non cases.

The mean duration of illness in the not sCJD group (n=44) was 26 months (range 4-108) (duration known in 43/44). Of those in the clinically suspected sCJD group ten had a duration of illness of six months or less. The diagnoses in this group were as follows:

Neoplastic/paraneoplastic disorders	5

normally used in immunocytochemistry. This is used to destroy the normal PrP (PrP^{C}) leaving the abnormal form of PrP (PrP^{Sc}) which is then detected using antibodies.

Alzheimer's disease	3
(including one patient with a diagnosis of AD and cerebrovascular disease)	
Cerebrovascular disease	1
Diagnosis uncertain	1

A comparison between disease duration in non cases and in sCJD can be seen in Figure 3.30. There were not any non cases with a disease duration of three months or less.

Clinical symptoms and signs in clinically selected non cases.

Myoclonus was reported in 28 cases with following diagnoses:

Alzheimer's disease (AD)	14
AD & CVD	2
Cerebrovascular disease (CVD)	3
Lewy body dementia	3
Encephalitis	2
Progressive supranuclear palsy	1
Chronic granulomatous encephalopathy	1
Multifocal calcifying leukoencephalopathy	1
Diagnosis uncertain	1

The presence or absence of specific clinical features was noted in all of the clinically-selected non cases, which gives a further indication of possible reasons why sCJD was suspected (see Table 3.26).

*** This figure includes three cases with both Alzheimer's disease and Cerebrovascular disease (CVD) which are not included in the total figure for CVD

Investigations in non cases

Thirty four of the 44 clinically selected non cases (77%) had an EEG recording. Upon review in the NCDJSU none of the recordings were sufficiently characteristic to be considered positive for sCJD (i.e. typical according to NCJDSU criteria outlined in Appendix 2). CSF 14-3-3 was tested in 15 (34%) and was positive in five cases, all with a final diagnosis of paraneoplastic syndrome. Cerebral MRI results were recorded in 18 (41%): ten were reported as normal, three were reported as showing atrophy only, three were reported as showing white matter ischaemic change only and two had both atrophy and ischaemic changes.

Cases with a final diagnosis of Alzheimer's disease

Alzheimer's disease is the most common alternative diagnosis in both clinically selected and unselected cases referred as suspect sCJD. The group of 20 patients in the clinically selected group with a final diagnosis of AD were analyzed separately to identify common factors.

The mean age at onset of these cases was 64 years (range 33-82 years, median 64 years). The mean duration of illness in this group was 42 months (range 6-108 months, median 33.5 years). Presenting symptoms were most commonly those of cognitive decline, seen in ten of the patients (50%). Other features at presentation were anxiety (n=3), difficulty mobilising (n=2) with headache, dizziness, loss of consciousness, paranoia, withdrawal, obsessive thoughts and weight loss each reported in one patient.

Myoclonus was seen in 16 (80%), pyramidal signs in 14 (70%) and psychiatric symptoms in 13 (65%). Other less common features included other involuntary movements (seen in 11 (55%)), cerebellar signs (seen in 6 (30%)), extrapyramidal features (seen in 4 (20%)), sensory disturbance (seen in 3 (15%)) and visual disturbance (reported in 2 (10%)).

The last patient to be referred to the NCJDSU and seen with a final diagnosis of AD was visited in 1998 and most of these referrals (n=18) occurred within the first five years of surveillance (i.e. pre-1995).

Table 3.23: Diagnoses in autopsy proven non cases, 1990-2002*

Diagnosis	Number of cases (n=182)
Alzheimer's disease (AD)	54
AD + Cerebrovascular disease (CVD)	4
AD + Lewy body dementia (LBD)	7
AD with amyloid angiopathy	1
AD with congophilic angiopathy	1
Lewy body dementia	23
LBD + CVD	1
Cerebrovascular disease	15
Multi infarct encephalopathy	1
Ischaemic damage + intracerebral aneurysm	1
Diagnosis uncertain	13
Neoplastic	
Metastatic cancer	5
Cerebral lymphoma	5
Limbic encephalitis	4
Primary brain tumour	2
Paraneoplastic cerebellar syndrome	2
Paraneoplastic syndrome with perivascular inflammation	1
Pick's disease (frontotemporal dementia)	5
Encephalitides	
Encephalitis	4
Encephalomyelitis	1
Viral encephalomyelitis	2
Subacute necrotising encephalitis	1
Non-specific encephalopathic features in the basal ganglia and thalamus	1
Post viral encephalitis/Landau Kleffner Syndrome	1
Herpes simplex encephalitis	1
Hypoxic damage	3
Progressive Multifocal Leukoencephalopathy	3
Progressive Supranuclear Palsy	2
Motor neuron disease	2
Corticobasal degeneration	2
Cerebral vasculitis	2

*Plus one of each:
Multi system atrophy, Hashimoto's disease, multifocal calcifying leucoencephalopathy, Multi system degeneration, amyloid angiopathy, widespread oedema and gliosis, corticostriatal nigral degeneration, multiple sclerosis, Wilson's disease, chronic granulomatous encephalopathy, Hepatic encephalopathy, Huntington's chorea.

Table 3.24: Neuropathological diagnoses in 44 clinically selected non- sCJD cases

Diagnosis	Suspected sCJD (n=44)
Alzheimer's disease (AD)	17
AD + cerebrovascular disease	3
CVD	4
Lewy body dementia	5
Progressive supranulclear palsy (PSP)	1
Metastatic cancer	3
Paraneoplastic syndrome/limbic encephalitis	4
Cerebral lymphoma	1
Multifocal calcifying leucoencephalopathy	1
Leukoencephalopathy	1
Chronic granulomatous encephalopathy	1
Diagnosis uncertain	3

Figure 3.27: Pie chart displaying the proportion of clinically-selected non cases with specific alternative diagnoses (n=44)

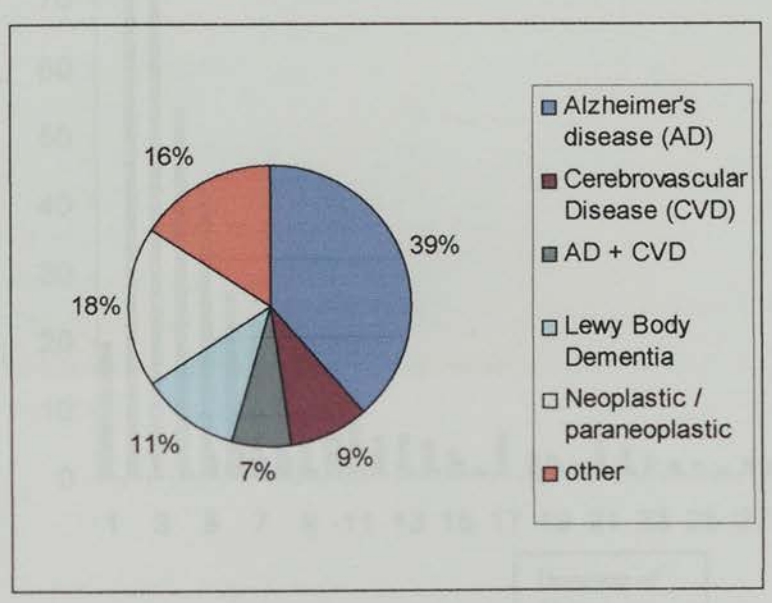

Table 3.25: Reasons cited as to why sCJD was suspected in non cases

(n=44)

Reason why sCJD suspected	Number of patients (% in brackets)
"Rapidly progressive dementia"	35 (80%)
Myoclonus	28 (64%)
Dementia plus cerebellar features	6 (14%)
Dementia plus pyramidal/extrapyramidal signs	4 (9%)
CSF 14-3-3 positive	5 (11%)
EEG considered positive	7 (16%)

Figure 3.28: Duration of illness in pathologically proven sCJD versus non cases

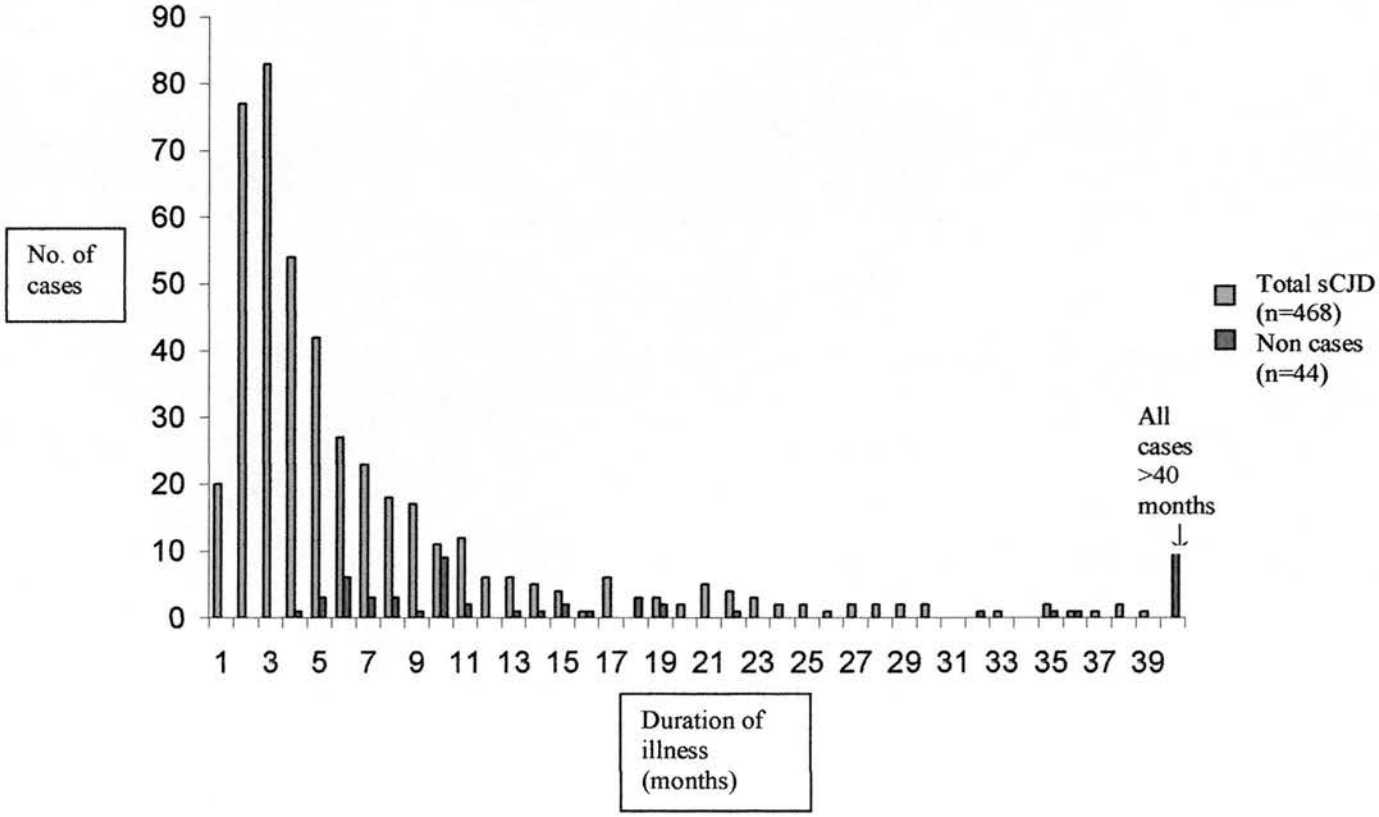

Figure 3.29: Scatter plot showing duration of illness in clinically-selected non cases (n=44) and total sCJD

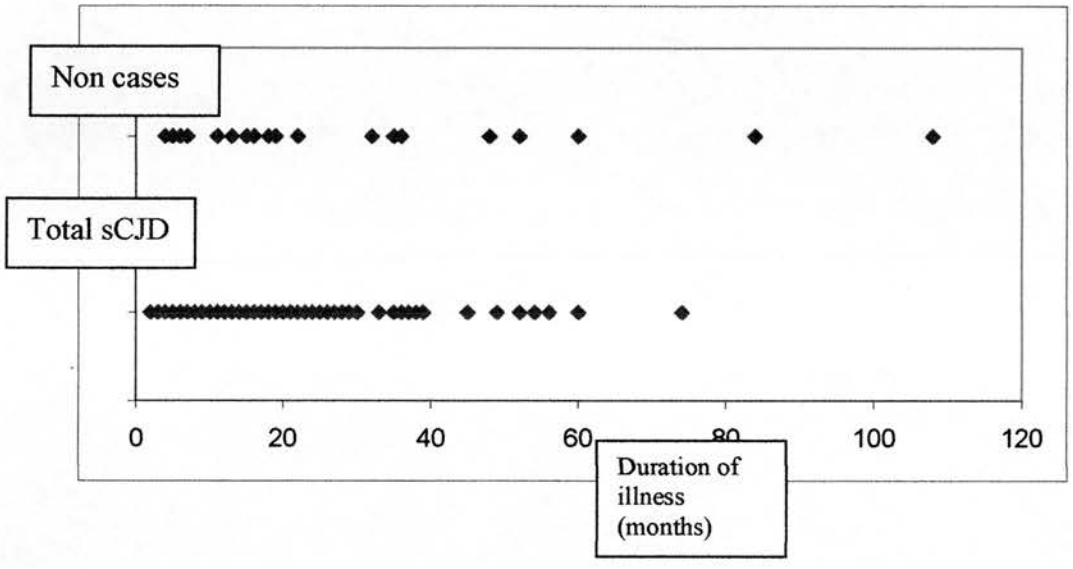

Table 3.26: Clinical features observed in clinically-selected non cases (n=44)

Clinical feature	% of Non cases
Pyramidal signs	73
Myoclonus	64
Psychiatric features	50
Involuntary movements	45
Cerebellar features	34
Extrapyamidal signs	32
Visual signs	27
Seizures	14
Sensory disturbance	11

Summary of findings in non cases

- The most common alternative diagnosis in non CJD cases referred as suspect CJD is that of Alzheimer's disease.
- Rapidity of cognitive decline and myoclonus are the most common reasons for a non CJD case to be referred as suspect sCJD.
- Most non cases have a longer duration of illness than that commonly seen in sCJD.
- In those with a duration of illness of less than six months the most common diagnosis is paraneoplastic/neoplastic disease.
- The typical phenotype of sCJD (short duration with myoclonus and a characteristic EEG) is sufficiently distinctive to request neuropathological review which in this study resulted in revision of the final diagnosis to sCJD in one case.

CHAPTER FOUR: DISCUSSION

This study has provided insights into the clinical manifestations of a rare neurodegenerative condition of uncertain cause. By describing the patterns of disease observed it aims to improve clinical diagnosis in the future. A comprehensive recognition of cases allows for more complete study of the disorder and of potential aetiological factors.

The study population and the documentation of symptoms and signs

This study involved only cases of sCJD that had been neuropathologically confirmed. Although this ensures complete accuracy in terms of the diagnosis there are potential biases involved. Cases of sCJD may be more likely to undergo an autopsy or brain biopsy if they are clinically unusual or the diagnosis in life is uncertain. Younger patients may be over represented, as autopsies in the elderly are less common*.

This study relies on clinical data collected by several different observers. Since the foundation of the surveillance unit in 1990, relatives have been interviewed and patients examined by 11 observers, each an NCJDSU consultant neurologist or research neurology registrar (with each research registrar recording data for a period of approximately two years). Efforts have been made to standardize the information gathered by the use of two proformas for the recording of clinical signs (one pre-1997, one introduced in 1997). The latter proforma allows for greater uniformity of data as symptoms and signs are specifically recorded along with their date of onset

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* As recorded by the Office of National Statistics for England and Wales

(Appendix 3). The earlier proforma does provide an outline for the recording of clinical details although it is less structured. The use of these proformas is likely to minimize variations in the quality of the data recorded for each patient. It would not, however, completely dispel the inevitable variation in interpretations of clinical symptoms and signs by each observer of the patient's clinical state. However, continuity was provided through individual case discussion with one of the two members of consultant staff (one of whom had worked at the NCJDSU since 1990 and the other since 1996).

Emphasis has been placed on the presence or absence of physical signs. If a clinical sign has not been recorded in the medical notes or observed by the visiting NCJDSU doctor it cannot be taken to mean that it was definitely never present. Often, after a diagnosis of CJD has been given, the emphasis turns toward palliative care and the patient may not be examined neurologically again. If for example, myoclonus only develops at this late stage in the illness it may never have been recorded as present. In this study, for practical purposes, if a clinical symptom or sign has not been recorded then it is regarded as absent because this reflects the realities of clinical practice. Therefore "absent", "not sure" and "unable to ascertain" were recorded together. It is possible that some of the "absent" or "not sure" responses may have been recorded in patients who did actually have the clinical sign in question but in whom it had not been elicited at the time of documentation. This may lead to an under representation of certain signs. This effect should be equal across subgroups. It could be argued that those in whom the diagnosis is uncertain are more likely to be examined repeatedly therefore increasing the accuracy of detection of clinical signs in more unusual cases. On the other hand, a more certain diagnosis may lead clinicians to elicit signs typical of the illness.

Classification of extrapyramidal signs may cause particular problems, as the wide range of prevalence in different studies demonstrates (Table 1.3). Parkinsonism is difficult to elicit in patients with sCJD as many cannot speak, write or walk. Increased tone in the limbs may take the form of spasticity rigidity or "gegenhalten" paratonic rigidity. The categorising of gegenhalten rigidity in the limbs (as either pyramidal, extrapyramidal or other) has varied in previous studies and in also in material produced from the NCJDSU[88] and could therefore be thought of as largely unreliable. In this study extrapyramidal signs are recorded as being present if the observer specifies "extrapyramidal signs /Parkinsonism present" or if bradykinesia, resting tremor or rigidity (not gegenhalten) are mentioned. Gegenhalten rigidity has been considered separately as it is generally thought to be indicative of frontal lobe disease[208]. The features observed in this study are compared with those seen in other studies (Table 3.4). The presence and absence of certain symptoms may depend on whether the relatives of the patient concerned were specifically asked about their presence or absence. The use of the standardised proforma would be expected to minimise error caused by the failure to ask as clear prompts are used. The consultant staff at the NCJDSU have had consistent and uniform views on these issues since 1990 (personal communication, Richard Knight). This study is likely to be more accurate than many previous studies looking at clinical features as most of the patients here were assessed in life by a surveillance neurologist. Retrospectively collected data from varied sources is fraught with bias and casts doubt on the validity of some of the earlier work.

The date and nature of disease onset may be difficult to ascertain. Onset is important as it provides information about disease duration and allows an assessment of early symptoms and signs. This is crucial in identifying Atypical cases according to our criteria. Information about disease onset aids subsequent work on pathogenesis and

susceptibility to disease of certain individuals. Often a NCJDSU doctor is able to visit the family and time, often lacking in the busy schedule of the ward doctor, can be taken to elicit a detailed history. The prospective gathering of information in this manner is likely to increase the accuracy of the clinical history obtained. Clinical information varies depending on whether the patient has close family or friends who have observed the early stages of the illness. If a family is visited after the patient has died the information received may not be as accurate as time will have elapsed. Conversely, it could be, however, that reflection by family members may improve accuracy as regards disease onset. They may recall early symptoms that initially were not thought to be relevant. Sometime the distress of family members may lead to difficulties in spending time over obtaining a detailed history and this may be aided somewhat by the passage of time. Obtaining a history after the death of the patient, therefore, may not have a uniform affect on the quality of information obtained.

The figure obtained in this study of 31% presenting with cognitive decline is comparable to that seen in other studies (see Table 3.2). Occasionally there have been significant difficulties in establishing the disease onset, for example if previous alcohol abuse had been a problem or if there was co morbidity in the form of psychiatric disease. These difficulties were experienced in the minority and because of the dramatic decline often witnessed it was frequently possible to get a clear history of the very first symptom from the relatives. Often clinicians call upon the NCJDSU for an opinion regarding an unusual patient and a comprehensive knowledge of presenting features allows for a more informed response in questions related to the early stages of the disease.

A previous study has examined cases of sCJD which presented with a "stroke-like" onset. This was not a common scenario at presentation in this study and when a

mistaken diagnosis of stroke did occur it was often soon corrected when a more detailed history was taken (e.g. of progression after the initial event). That is to say, the figures presented may have been an artefact of inaccurate history taking.

In order to identify cases for this study the author reviewed the complete NCJDSU archive of pathologically proven cases on two occasions to identify patients who met the criteria for study. The use of one observer eliminated the problem of observer variability in selection and repeating the procedure minimised any chance that information had been missed.

Atypical cases

What is the value in defining and studying them?

Clinical heterogeneity in sCJD has long been recognised[64;65;69;125]. This study has sought to clarify the extent of this variation and identify cases that cause particular diagnostic problems. Clear distinctions made by definitions of "an Atypical case" may be somewhat misleading. Definitions rely on fixed boundaries when in reality what exists is a clinical spectrum of disease. In long duration cases for example a patient with an illness duration of 24 months is Atypical (according to the definition used in this study) whereas a patient with a disease duration of 23 months is not. There are therefore limitations in the process of attempting to define Atypical and some unusual cases may fall outside of the boundaries of a definition. Despite this, defining Atypical groups does allow for the identification of many cases at the "end" of the phenotypic spectrum that are likely to add to our understanding of the variation which exists in disease phenotype. With about one quarter of all pathologically proven cases

of sCJD meeting the definition of Atypical used here it is clear that clinical heterogeneity is not insignificant. It follows that if too rigid a view of the clinical picture in CJD is adhered to cases are likely to be missed. The description of the full spectrum of disease in sCJD is important in improving the accuracy of disease surveillance by enhancing case recognition. An understanding of the variety of clinical presentations may increase the accuracy of early diagnosis. Accurate diagnosis of CJD is important in counselling families and providing appropriate care for patients. It allows for a prediction of disease trends and an assessment of geographical distribution of cases. In the past, where unusual cases have caused diagnostic difficulties, brain biopsies or other invasive procedures may have been performed without adequate safety precautions, carrying with them the inherent risks of onward transmission of the infective agent.

An appreciation of the spectrum of clinical features within sCJD will allow for assessments of any change in the phenotype over time. This is particularly important if vCJD cases with a MV or VV genotype at codon 129 are to emerge. A clear description of the phenotypic variation in sCJD in the UK would allow for a comparative study with other countries where a surveillance system exists and thus to identify phenotypic variation with different environments.

Observed phenotypic variation in sCJD

Correlations between age[9;65], duration of illness[64;65] and clinical features have already been highlighted in previous studies. This work builds on those observations by studying subgroups defined by the following characteristics from a large cohort: Duration of illness of greater than two years

Age less than 50 years at disease onset

Onset with visual symptoms in isolation for at least the first two weeks of the illness

Onset with cerebellar features in the absence of cognitive decline for at least the first month of the illness

Onset with other focal features (and no documented cognitive decline for at least the first month)

Relatively distinct features found in each of the Atypical subgroups studied are shown in Table 3.20a and 3.20b. These should aid in the recognition of these more unusual cases in the future.

Why is phenotypic variation observed in sCJD?

It remains somewhat unexplained why differences in clinical phenotype should occur. Certainly there seems to be a relationship with genotype at codon 129 of the PRNP gene which has been highlighted by several studies. The current study has described relatively distinct characteristics of subgroups of sCJD. Although there does appear to be a relationship with differing genotypes in some of these groups it is only the visual onset group that correlates fully with one genotype (MM). It should be stressed, however, that numbers did not reach statistical significance when compared with the distribution of genotype observed in the core group. Genotype and prion strain influence the pathological distribution of abnormal prion protein[87] and some of the focal features at onset are likely to relate to prion distribution in focal areas. In the current study, prion strain data was incomplete and has not been discussed further because of this limitation.

In addition, it is possible that there may be some hitherto unidentified environmental factor that influences phenotype. Work looking at the geographical distribution of atypical cases has not been performed. An interesting starting point to examine this further may be to compare the UK data on phenotype with that seen in other European countries. Epidemiological data including occupation, places of residence and previous medical history is collected for each case and this couldbe examined further to see if patterns emerge within subgroups. So far, however, work looking at causes of CJD from this data has not yielded consistent risk factors and any possible associations with different phenotypes remain purely speculative. The route of acquisition influences the clinical picture in iatrogenic CJD and it remains possible that, if sCJD is acquired from an external source (which in itself is controversial), routes of infection may influence phenotype.

The genotype in the young may vary because of the way that the young brain responds differently to abnormal prion protein compared with the ageing brain. The prominent early psychiatric features (also seen in vCJD) may partly reflect the tendency to detect subtle early symptoms in the young that may be overlooked in the elderly. There may be a greater capacity to compensate for diseased regions in the younger brain explaining in part the known association with longer disease duration observed in the young.

It should be acknowledged that genetic CJD was not excluded in all cases therefore raising the possibility, albeit unlikely, of genetic CJD. This has previously been described as causing a longer illness duration in younger patients, at times with prominent cerebellar features at onset.

Young cases.

These cases receive particular attention because dementia in the young is so unusual and devastating. In addition, because of the age of these patients vCJD is more often considered. For many in this group the duration of their disease is considerably longer than that typically associated with sCJD and in nine of the 34 identified cases it exceeded two years. Reasons for the association between a young age at onset and a longer duration of illness have been commented on in the introduction to this thesis. These include the detection of subtle early symptoms in the young (that may have been attributed to the processes of ageing in the elderly), the tendency to use artificial feeding more often in the young that may prolong life and the fact that the elderly often have other medical problems that may hasten a decline.

Psychiatric features are more commonly associated with young cases than with a comparison group of Core sCJD and may raise the clinical possibility of vCJD [209]. A higher incidence of psychiatric symptoms in the young may partially reflect the tendency to notice more subtle symptoms in young people and also the fact that many of the younger patients were living with a spouse who would be likely to detect disorders of mood or affect compared with the older patients where a higher proportion may be widowed or living alone. Any features more commonly noted in the young could be due to a closer observation in this age group, including the finding that involuntary movements were more common. Both psychiatric features and involuntary movements are prominent in vCJD (predominantly a disease of the young) and the findings in this study may reflect how the younger brain responds to prion disease. This study has shown that vCJD was considered in some of the young cases but only exceptionally was it the preferred diagnosis. At times where there is

clinical confusion, a brain MRI (looking for the "pulvinar sign") or a tonsil biopsy (to detect PrP^{Sc}) are useful procedures in distinguishing sCJD and vCJD as both are sensitive and specific for vCJD. The MRI has the advantage of being non-invasive, although if there is no pulvinar hyperintensity the tonsil biopsy is a useful tool.

Cerebellar features are less commonly observed at onset or throughout the illness in young cases when compared with Core sCJD. The fact that young cases are likely to be closely observed makes this unlikely to be due to under ascertainment of clinical features. None of the cases that presented with virtually isolated cerebellar features were aged below fifty years at disease onset but they were as a group significantly younger than the mean age observed in the Core group of sCJD patients. Previous studies examining cerebellar pathology in sCJD have demonstrated that abnormal PrP deposits are observed in clusters that appear to be distributed along anatomical pathways[210] and that the codon 129 genotype affects the accumulation of PrP^{Sc} in the cerebellum[211]. Valine homozygosity is more commonly associated with cerebellar features and is also associated with a younger age at disease onset which appears to be reflected to some extent in the cerebellar onset cases identified here. There is no obvious explanation, however, for the lower incidence of cerebellar features observed in the young cases of sCJD or the younger than average age observed in the group presenting with virtually isolated cerebellar features.

CSF 14-3-3 was the most sensitive investigation in young cases, with just over 70% of those tested (n=17) yielding a positive result. In these cases it is less sensitive than generally recognised in sCJD[164]. Young cases tend to have a longer duration and as CSF 14-3-3 is a marker of neuronal loss it is more likely to be negative if the neuronal loss is more protracted. The cerebral MRI has a comparable sensitivity in this

context, at 56% (n=9), to that seen in sCJD as a whole[127] but the EEG, being positive in only 13% (n=31) was less sensitive.

It is likely that problems with case ascertainment are, on the whole, less significant in the young compared with the old. The exceedingly high profile of vCJD as a dementia predominantly of the young is likely to have raised awareness of CJD generally in young people with dementia. People dying under the age of 50 are more likely to have an autopsy than older people and a couple of "look back" studies (primarily designed to detect any missed cases of vCJD) have failed to demonstrate under ascertainment of CJD in the young[26;27]. Increases in case numbers have been largely in the over 65 age group since prospective surveillance began in the UK[195]. This is thought to reflect improved ascertainment in the elderly but nonetheless fewer cases are observed in those over 70 years of age (see Figure 1.2) than between 65 and 69 years of age. This may be due to a true decrease in the disease in the very old or alternatively a failure to detect disease in this age group. It has been demonstrated in this study that the majority of those under fifty with pathologically proven sCJD are both suspected in life and referred to the NCJDSU prior to death (albeit after a longer period of time than that observed in Core sCJD). Of the two young cases that were not suspected in life as having sCJD both had a duration of illness of greater than three years which may have contributed more than the young age to the fact that diagnosis was missed in life. In view of the association with long duration it cannot be assumed however that all young onset cases will be recognised, since those with a long duration are possibly the most difficult to detect.

Long duration cases.

This group includes some of the most unusual and most difficult to diagnose sCJD cases. This is reflected in the fact that this group has the highest proportion of autopsy-only diagnoses than any of the other Atypical subgroups or Core sCJD. Even those neurologists who are most experienced in recognising CJD may fail to make a diagnosis in such cases. If surveillance is to effectively identify unusual cases then unusual referrals should be followed up. Surveillance neurologists should not adhere to too rigid a view of what a case of sCJD consists of. This is likely to mean that more non-cases may be assessed but this is the only way to learn more about the spectrum of disease in the most unusual cases.

Personality and behavioural change along with depression are significantly more common at onset in long duration cases than in a comparison group of Core sCJD cases. This is important to highlight as these features are generally more associated with the onset of frontotemporal dementia[212] or Alzheimer's disease[213]. Indeed, the most important differential diagnosis in the long duration cases is Alzheimer's disease.

One of the difficulties in making an assessment of disease progression in long cases is the lack of good quality follow up data. If a patient is seen in life by a NCJDSU doctor then information is only reliably available up until that point and may not be provided for the remainder of the disease duration. However, from a review of the available clinical data in the NCJDSU archive it was possible to ascertain whether individual long duration cases were truly slowly progressive or whether patients were being sustained for a long period in a nursed and fed, akinetic and mute state. In the majority, disease progression was generally much slower than that typically witnessed in shorter duration cases (with only two of the 28 patients losing the ability to walk within one year). This is in keeping with the findings of the largest

published cases series of 33 cases[65] with an illness duration of two years or more*. In the study by Brown et al only three out of 15 patients deteriorated rapidly over a period of several months and then were sustained in a physically dependent state. The remainder displayed a more slowly progressive course. The longest period that any patient in the current study was maintained in a bed bound, fully dependent state was 50 months. This individual was highly unusual in many respects and was the youngest patients known to the NCJDSU with sCJD**.

An important differential in the eleven long duration cases without genetic analysis is that of genetic CJD, as this is often associated with a more protracted disease course. None of these patients however had a family history of a CJD-like illness but it is acknowledged that this is far from conclusive evidence of a sporadic rather than genetic form of the disease.

A particular difficulty with long duration cases is that, according to current clinical criteria, none of the cases studied here meet the definition for a case of sCJD. Cases with a duration of illness greater than two years are automatically excluded unless they have a positive EEG (Table 1.8). If the case definition were expanded to include those with a long duration of illness (regardless of the EEG result) a likely consequence would be a decreased specificity of the case definition criteria. Alzheimer's disease and other neurodegenerative conditions may also meet the definition for a Possible case if this occurred.

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* This study included ten familial cases.

** The neuropathology on this teenager was reviewed following the emergence of vCJD and found to be negative for the features associated with this disease.

Despite the Atypical phenotype, over 60% of long duration cases were referred to the NCJDSU in life. One of the difficulties in making a diagnosis in these cases is that the investigations traditionally relied on to aid clinical diagnosis in sCJD are often less sensitive. This was a particular problem with the EEG where it was uncharacteristic in all 22 of those tested. A low sensitivity of the EEG has been observed before in long duration cases[65]. Several factors, including the degree to which sCJD is suspected, may influence this. For example, in a short duration, clinically typical case a clinician may expect to see a positive EEG and arrange for repeat tracings to be taken at time intervals until this appearance is seen. In long duration cases the diagnosis may be considered unlikely because of the unusual phenotype and therefore any efforts to elicit repeat recordings may be considered futile. It may also follow that if a single EEG is performed in a long duration case it is likely to be taken at a fairly early stage of the illness when a patient is under investigation. In this study 14/28 (50%) of long duration cases were clearly documented as being mobile at the time of the final EEG and none of the cases had an EEG in the final month of the illness. Amongst the Atypical cases in this study a positive EEG correlated with an older age at onset and shorter illness duration. Early EEGs are less sensitive at detecting the characteristic appearance of sCJD[142;145;214] and in our study and others[215] there is a correlation with physical dependence and a positive EEG. In other work an association between shortened survival[125] and periodic sharp wave complexes (PSWCs) on the EEG has been found. All clinically Atypical cases, of any category, with a positive EEG (who had genetic testing) had an MM genotype at codon 129 and this supports previous observations[87].

The rare combination of Alzheimer's pathology with sCJD[122;123] was not an explanation for the long duration in any of these cases (neuropathology reports were

reviewed individually) and a complete explanation for the protracted nature of their illness remains unknown.

Pure visual onset cases

This study has highlighted that judging cases to be Atypical or not by certain features at presentation may not necessarily identify clinically unusual cases. Three groups were defined in this way: those with a pure visual onset, those with a cerebellar syndrome at onset and those with a delay in the onset of a cognitive decline (associated with another focal onset).

In previous studies patients defined as "Heidenhain" cases have represented up to twenty percent of sCJD cases[82] but definitions have varied from isolated visual symptoms at onset[216] to cases with a mixed presentation of visual and other symptoms[82]. Heidenhain's original three cases did not present exclusively with visual symptoms, in fact one of the cases did not have a visual disturbance at all[72]. This study sought to clarify a practically useful definition for "Heidenhain cases" by focussing on those presenting with visual symptoms *in isolation*. It was thought that cases presenting in this way may pose particular early diagnostic problems and/or raise specific public health issues relating to eye surgery[60;217] and therefore provide a substantial reason for identifying them as a subgroup. Very early recognition of visual onset cases probably rests with ophthalmologists as the majority were referred to this speciality initially. However, when pure visual onset cases were examined, apart from the early part of the illness, they generally exhibited a typical disease course and were diagnosed relatively early on compared with Core sCJD cases. The duration of illness was shorter than that

seen in Core sCJD and the rapidity of decline was often striking. It could be said that these cases were in some respects the most "typical" of the sCJD subgroups studied. Notification to the NCJDSU was prompt and overall diagnosis was rarely delayed beyond two months. The potential remains for needless intervention in the form of eye surgery[218] if the disease is unrecognised in the early stages and this occurred in two of these cases. As PrP^{Sc} has been detected in the eye[219] any intervention involving ocular tissue may pose a risk for onward transmission of the agent.

The visual onset group identified in this study exhibited less cerebellar or extrapyramidal signs than a comparison group of Core sCJD cases. This may reflect the very short duration of illness seen in most visual onset cases where clinical features are engulfed in a rapid decline with a loss of the cooperation often required to elicit cerebellar or extrapyramidal features.

It is important to emphasise that in the current study pure visual onset cases were identified without prior knowledge of genotype (i.e. cases were identified by a review of the clinical history only). This eliminated selection bias to prove or disprove any interaction between genotype and phenotype and the subsequent associations shall be discussed below.

Based on the findings in this study there is little clinical basis upon which to regard these cases as representing a "variant" of sCJD apart from the presenting symptom (which does not appear to be a barrier to accurate diagnosis). The term "Heidenhain variant" may also be misleading in view of the emergence of vCJD. In many respects these patients are clinically typical for sCJD and, although

cognitive decline may be delayed at first, visual symptoms appear to be a marker of a particularly rapid form of the disease.

Those with a cerebellar syndrome at onset

Relatively isolated cerebellar features at onset are well recognised and in that sense not likely to cause *prolonged* diagnostic difficulties in those experienced in diagnosing CJD. However, in the early stages of the disease the differential diagnosis may be wide and sCJD is often not considered until a dementia supervenes. A paraneoplastic cerebellar syndrome is a relatively important differential diagnosis especially as it may be accompanied by a sensory peripheral neuropathy and sensory features were relatively commonly observed in this group.

Amongst those presenting with an isolated or relatively isolated cerebellar syndrome (without an initial cognitive decline) statistically significant association with sensory symptoms was found (in three cases they were recorded in the very early stages). In two of Brownell and Oppenheimer's four original cases (that first drew attention to a cerebellar syndrome at presentation in sCJD) sensory features were prominent. Cases with a virtually isolated cerebellar onset often exhibit a striking delay in cognitive decline. In this study, delays in the emergence of a cognitive decline were observed as much as six months after onset. The increased reported incidence of both visual and sensory symptoms in this group may in part reflect preserved cognition (i.e. the retained ability to recognise and complain of an unusual experience).

An important differential diagnosis in this group is that of genetic prion disease (eg GSS) which may also present with a cerebellar syndrome and this was not excluded with genetic analysis in ten cases. None however, had a family history of CJD.

More men (n=17) than women (n=8) were observed as presenting with virtually isolated cerebellar features. This difference was not statistically significant. There was a significant difference in the ages observed in the pure cerebellar onset group compared with Core sCJD (the pure cerebellar cases were younger). This correlates with the observation that the distribution of codon 129 genotype was significantly different in this group (more VV, more MV and less MM). VV cases have been noted previously to be associated with a younger age at onset[87;211]. Once cognitive decline was noted these cases followed a fairly typical clinical course for sCJD.

Investigations including CSF 14-3-3 and MRI were useful in this context. The MRI displayed a sensitivity of 80% (eight out of ten patients had a positive scan) and the CSF 14-3-3 was positive in 83% (ten out of 12 patients). The EEG was positive in only 12% (three of the 25 patients tested). This may relate in part to EEG timing as ten of the 25 patients (40%) were still walking, albeit unsteadily, at the time of the last EEG recording. All three in whom the EEG was positive were bed bound with myoclonus at the time of the recording, which correlates with the previously discussed finding that the EEG is more useful in advanced disease [215].

Amongst the cerebellar onset group a relatively high number of cases were not referred to the NCDJSU in life (32%). It is worth highlighting the need to ensure ongoing education and debate amongst neurologists about different presentations in sCJD if surveillance is to retain or indeed increase its' accuracy. Once more the need to encourage referral of unusual cases should be emphasised.

Other focal features at onset in sCJD

Those presenting with another focal symptom (i.e. not visual or cerebellar) where a global cognitive decline is delayed represent an interesting and heterogeneous group. This study has highlighted less common presenting symptoms that have the potential to be misleading if they do not occur in the context of a global cognitive decline. One of the difficulties that arose when selecting patients to be included in this group related to the accuracy of the recorded information in determining whether or not early cognitive decline was present. Since 1997, each time a NCJDSU doctor assesses a patient they are asked to record the date of onset of a dementia. If there is a discrepancy of more than one month between the date recorded as symptom onset and the date recorded as dementia onset (and if this was backed up by the written clinical history) then a patient was regarded as having had a delayed onset of cognitive decline. Prior to 1997 a detailed clinical history was obtained and patients were included in this group if it was clearly stated that they were "cognitively normal", "not demented" or "mentally intact" at least one month after symptom onset. These differences in recording may partially explain why more patients in the focal onset group had a symptom onset after 1997 as they were often easier to identify. A criticism of this aspect of the study is that unless a patient has undergone detailed neuropsychological assessment it is virtually impossible to exclude any cognitive impairment. Also, early features of a cognitive impairment may include psychiatric features in isolation such as depression or anxiety. In defence of the method used here it should be stated that it is largely a pragmatic assessment of how clinicians view their patients. In reality, assessments of the presence or absence of cognitive decline are often made by speaking with close relatives and conducting simple bedside tests. It is accepted that it was virtually impossible to

exclude subtle cognitive impairment in those presenting with focal features. Patients were included in this atypical subgroup if there was clear documented evidence that clinicians, family and the NCJDSU doctor *did not perceive them as being cognitively impaired.*

The most common focal symptoms at onset in this group are sensory. Eight of the twelve with sensory features at onset had unilateral sensory symptoms (e.g. numbness in left side of face, left upper and/or left lower limb). This is likely to represent a central nervous system, rather than peripheral nervous system, pattern of sensory disturbance. In three cases the sensory symptoms were bilateral (tingling feet/burning feet/numb hands) but in the one of these who underwent electrophysiological studies no evidence of a peripheral neuropathy was detected. Since the emergence of vCJD, sensory symptoms may be more likely to be recognised in CJD as a whole. However, in terms of those who present with sensory features the numbers have remained fairly constant both before and after 1996 (implying that these are features that are volunteered by those giving the history and do not have to be specifically asked for). In vCJD it has been postulated that the sensory features at onset may represent a thalamic syndrome (mirrored in the pulvinar hyperintensity seen on cerebral MRI). There was no such pulvinar sign amongst these patients whose scans we were able to review. There were no reports from local neuroradiologists of the pulvinar sign being present in the MRI scans not reviewed at the NCJDSU.

Involuntary movements, without an early global cognitive decline, were uncommon being seen only in six patients.

Possibly the most unusual cases in this group are three patients who developed a flaccid quadraparesis. In one case fasciculations were noted and tendon reflexes, though maintained, were diminished. Despite accompanying sensory features the working diagnosis was of motor neuron disease. The second case had an illness characterised by extreme lethargy, depression and unsteadiness followed by a severe, flaccid weakness of the upper and lower limbs. This was associated with areflexia but fasciculations were not observed. Accompanying neurophysiology revealed a severe axonal peripheral neuropathy. The third case was characterised by early sensory symptoms followed by a progressive weakness of all four limbs. Tendon reflexes were maintained, being initially noted as brisk. Peripheral neurophysiology was not performed. Although lower motor neuron signs are well recognised in sCJD[115] the degree of weakness witnessed in these three cases is remarkable and caused considerable diagnostic confusion (two were diagnosed at autopsy and one after a brain biopsy). Unfortunately as the peripheral nervous system was not examined at autopsy in any of the cases further elucidation of the pathological processes was not possible but these cases raise questions as to the effects of disease on the central and peripheral nervous system. Why such unusual cases would occur remains poorly understood and highlights the importance of neuropathological examination in detecting cases that are so far removed from the "typical" disease phenotype.

Although there are problems in considering cases as Atypical on the basis of presenting features alone, in terms of enhancing early diagnosis this may be useful. Raising awareness of certain patterns of presentation, including those that are rare, may aid early recognition of cases that previously have eluded diagnosis until a rapidly progressive dementia ensued. In some instances, despite the presence of a dementia, an unusual onset may preclude the diagnosis being made. A description of

the spectrum of presentation may allow for sCJD to be recognised where previously it may have been discounted with "sporadic CJD never presents like this". Early diagnosis is important in terms of provision of care and appropriate counselling for families as well as enabling relevant public health measures to be implicated. In the past, failure to recognise more unusual phenotypes at presentation has led to the reuse of potentially infected surgical instruments.

Evidence has accumulated to demonstrate that different codon 129 polymorphisms affect phenotype[87;220;221] and this research supports some of the findings by identifying patients on the basis of phenotype whilst blinded to genotype. The effect of PrP^{Sc} isotype may act independently of codon 129 genotype (e.g. an association with type IIa prion protein and prolonged survival[15]). The potential role of geographical and/or environmental factors in determining phenotype should be explored. Previous studies have alluded to small geographical clusters of sCJD[222-224] but it is yet unknown if there is an association between clinical phenotype and geographical distribution. An interesting study would be to assess the frequency and nature of Atypical sCJD across Europe (i.e. in the EUROCJD and NEUROCJD collaborative groups). If this were to be undertaken however it would be imperative to standardise definitions and methods of collecting and interpreting data.

The codon 129 genotype in Atypical cases

The association with young onset cases and a particular genotype at codon 129 and glycotype (where known) is not clear cut amongst our patients. Parchi et al found that those with a VV2 or MV2 genotype/glycotype were likely to be younger[87]. In the young cases studied here the most common genotype was MM. Three young cases

were MM1 (a genotype/glycotype combination that Parchi found to be associated with an older age at onset).
In terms of the genotype in the long duration cases studied here, data were incomplete (11 not having genetic analysis performed) but there was a slight excess of MV cases, a finding that has been observed before in those with a longer disease duration[87]. There were not any MM1 or VV2 cases in this group (which would fit with the hypothesis of these genotype/glycotype combinations being associated with short duration). It should be pointed out that glycotype data was not available on two MM cases and three VV cases.

All tested visual onset cases had an MM genotype, with a type 1 glycotype where known. MM1 sCJD is associated with typical clinical features[87]. In this study pure visual onset cases have been labelled as Atypical but it has become clear that they soon evolve into a generally typical sCJD phenotype and it is the onset of disease only that is unusual.

There was a slight excess of patients with the VV genotype in the pure cerebellar onset group (predominantly VV2 in keeping with the association that Parchi described between this group and an ataxic onset[87]). Patients were identified on the basis of clinical features alone whilst blinded to genotype at the time of selection. In contrast to Parchi's work we did find a VV1 case presenting in this way (he found ataxia to be "completely lacking" in this subgroup[87]). The codon 129 genotype was known in only five of the ten presenting with sensory symptoms at onset. In four cases it was MM, in one VV.

The MRI in Atypical cases

The finding of high signal in the basal ganglia was not significantly different between Atypical sCJD and cases without Atypical features. In addition correlations between specific clinical features and basal ganglia high signal were not detected. For example, those with documented extrapyramidal features were not more likely to display basal ganglia abnormalities. It remains unclear why some patients display diagnostically useful features on cerebral MRI whilst others do not. In some previously studied patients serial MR brain scans showed an increase in hyperintense signal in the basal ganglia over weeks to months[127], whereas in other publications no increase in hyperintense signals were noted over time[225;226].

The cerebral MRI was positive in four out of six long duration cases where the scans were available for review and, although numbers are very small, it may indicate that this is a useful diagnostic test (especially as the EEG and CSF 14-3-3 lack sensitivity in this context). More work is needed to clarify this with larger numbers.

Sporadic CJD as a differential diagnosis of vCJD

Despite the distinct phenotype that is associated with vCJD, on occasion patients with sCJD have been thought to have vCJD[170;227]. Young age at onset appears to influence the perceived likelihood of vCJD as oppose to sCJD. This study has demonstrated that young cases of sCJD manifest more psychiatric symptoms than a comparison group of Core sCJD cases. Other features such as ataxia, myoclonus or psychiatric features later into the illness are common to both diseases and unlikely to favour vCJD. Known patients with vCJD have fairly uniform pattern of clinical

presentation and progression [25;37] which is unlike the phenotypic variation observed in sCJD.

Sensory features are common in vCJD and are also well-documented in sCJD. In previous studies the incidence was between seven and 16 % at some point in sCJD [64;67;228]. Our study found sensory features to be present at between 10% (Core sCJD) and 70% (Focal onset sCJD). It is possible that since the advent of vCJD sensory features are more commonly sought after and recognised in sCJD, although for those with sensory features at onset an equal number were recorded before and after 1996. Whereas in vCJD sensory symptoms possibly represent a thalamic pain syndrome (reflected in the hyperintensity seen in the thalamus as the pulvinar sign) [36] in these sensory onset cases no such thalamic abnormalities are detected on MR imaging. Brain MRI findings early in sCJD generally point to a more cortical involvement[98;138], rather than the basal ganglia abnormalities seen in vCJD.

Underpinning the clinical diagnosis of CJD are internationally agreed case definitions. A diagnosis of Probable sCJD has a positive predictive value of 97%[145] whereas a diagnosis of Probable vCJD has not yet been disproved at autopsy (personal communication, James Ironside). No cases of sCJD to date have met the clinical criteria for a diagnosis of Probable vCJD. The high specificity of the classification of Probable vCJD relates largely to the pulvinar sign on brain MR imaging which is a sensitive and specific marker of vCJD[38]. Case reports are emerging of the potential for confusion when interpreting MR scans in this context and there is a need to use the clear definition of the exact nature of the abnormality[229-231]. Periodic sharp wave complexes on the EEG have not been reported in vCJD and their presence should help to distinguish between the two diseases.

Cases referred after autopsy: issues in underreporting

These cases are important because they highlight areas where clinical surveillance of CJD fails. As autopsy rates in the UK continue to decline it is important that every effort is made to enhance diagnosis and referral of cases in life. Underreporting may adversely affect public health efforts by distorting trends observed by incidence of disease, risk estimates for disease acquisition and the geographical distribution of cases.

Surveillance in the elderly: cases referred after autopsy

This study has demonstrated that cases referred after autopsy are older than those referred in life. In other words, age influences whether or not patients with sCJD are detected and referred to the NCJDSU whilst they are alive. It is known that autopsies are carried out infrequently in the elderly and this raises concerns that cases are being missed i.e. if the autopsy is not done the case will not come to light. The decline in numbers of sCJD seen in the elderly (Figure 1.3) cannot be assumed to be due to a true decrease in case numbers but may reflect underascertainment.

Cases where the diagnosis was not suspected in life

By examining these cases it should be possible to highlight features that cause particular diagnostic difficulties and areas where clinical surveillance may be improved upon. Several possible explanations why there is a failure to diagnose sCJD in life have emerged from this study and include:

The clinician does not recognise the phenotype of the disease because they are unfamiliar with sCJD and how it manifests

The clinician (who may be familiar with "typical" sCJD) does not recognise the disease phenotype because it is unusual and does not fit in with their perception of what constitutes a case of sCJD

The patient has pre-existing medical problems which cause confusion and to which the illness representing sCJD is attributed

It is not possible to gain an accurate history of the disease course

Investigations relied upon to aid the diagnosis of sCJD are negative

For the first two scenarios it should be possible to increase diagnostic accuracy by increased education amongst relevant clinicians regarding the nature of the disease.

Unfamiliarity with sCJD.

If it is assumed that a rapidly progressive dementia with death by six months should at least raise the possibility of the diagnosis in a clinician familiar with the phenotype in sCJD then a lack of experience may have played a part in 12 cases (2.5% of total sCJD). In four cases a neurologist had assessed the patient. This may of course have related to factors other than a lack of familiarity with the condition (for example, pressures of time when asked to give a second opinion, a lack of available information regarding disease onset and course).

Maintaining a high level of awareness of the features associated with a condition is essential for effective disease surveillance. It is difficult to imagine how CJD could have achieved a higher profile amongst the medical profession than that experienced as a result of the emergence of vCJD in 1996. Further analysis of the more typical

missed cases indicates that six of them were unwell in the period following the emergence of vCJD (1996-2002) and six died prior to 1996. Looking at unsuspected sCJD cases as a whole it is interesting that the highest number were recorded in 1998 when general interest surrounding CJD was probably at its height. More cases were likely to have been detected because of a peak in the post-mortem examination rate amongst referrals to the NCJDSU at just over 80%. This suggests that in other years cases were missed because of lower autopsy rates. It is perhaps surprising that in 1997, shortly after the emergence of vCJD, six *suspected* cases of sCJD were not referred to the NCJDSU. One reason for this may be that the perceived focus was so strongly on detecting vCJD that the importance of referring sCJD cases was overlooked. Currently autopsy rates for all referrals to the NCJDSU stand at about 65% (as part of a declining trend). This decline forms part of a decrease nationwide in all autopsies and is likely to mean that cases that would previously have been diagnosed on autopsy only will be missed.

There are a similar number of Atypical cases amongst those referred after autopsy and those referred before autopsy. Less than forty per cent of clinically unsuspected cases exhibited Atypical features (according to the definition used in this study). There were no cases with a pure visual onset in the unsuspected group reinforcing the idea that these cases do not cause a great deal of diagnostic confusion except in the initial phase. The most frequently observed Atypical feature associated with failing to suspect sCJD was a long duration of illness. It is important that clinicians are aware that, although extremely rare, sCJD may cause a dementia lasting for greater than two years. Features which may point to a diagnosis of sCJD despite the long duration could include a rapid terminal phase, the presence of myoclonus and/or supportive investigations (especially CSF 14-3-3 or basal ganglia high signal

on brain MRI). The association highlighted in this study between long duration and young age should alert clinicians to the possibility of sCJD in younger patients.

Pre-existing medical problems may cause confusion.

Amongst cases only referred after autopsy three clear examples of confusion associated with pre-existing medical problems emerged. The first related to a prior diagnosis of terminal cancer, the second to the coexistence of Alzheimer' disease and the third involved a patient diagnosed with "ischaemic diabetes mellitus-related cerebellar degeneration". It is perhaps surprising, especially in the first two cases, that an autopsy was carried out at all and it is unknown how many other cases are misdiagnosed in this manner without autopsy.

Negative investigations in unsuspected cases.

Of the 26 patients who were not suspected of having CJD whilst alive, 11 (42%) had an EEG recording. None of these patients had an EEG recording that would have been regarded as typical/positive. None of these unsuspected cases had CSF 14-3-3 examination. Referral for CSF 14-3-3 implies that the diagnosis of CJD is suspected. Findings on brain MRI are poorly documented in these cases.

Cases suspected but unreferred in life

Unreferred cases are an inevitability of any surveillance system but efforts should be made to encourage maximum referral. Of the Atypical cases in those referred after autopsy (n=21), 12 (57 %) were suspected of having CJD whilst alive. This suggests that in a suspected case Atypical features may deter referral

to the NCJDSU. Clinicians may only feel happy to refer a case if they are fairly certain of the diagnosis and Atypical features may diminish this. It is important that clinicians appreciate that there is, at times, a diverse phenotypic spectrum in sCJD.

It is often difficult to be sure from the medical notes exactly why a referral was not made, as details regarding this are often not recorded. In previous studies of other disease surveillance, common reasons for non-referral included not knowing how to report, concerns about confidentiality and a perception that too many diseases encountered in clinical practice required reporting[191]. An assumption that someone else would have reported the patient with suspected sCJD was a factor in some cases in this study (for example the neurologist assuming the medical team would make the referral and vice versa).

It is unlikely that any neurologist in the UK has not heard of the NCJDSU but not every patient with CJD comes into contact with a neurologist. Yearly reminders are circulated not only to all neurologists but also to neurophysiologists and neuropathologists. Of those cases not seen by a neurologist (where perhaps the awareness of the NCJDSU and the criteria for referral are less clear) general physicians and psychiatrists were most likely to have been the only specialists to have made an assessment of the patients (alone assessing 13 and 7 of the total number of 91 unreferred cases respectively). The presence of these patients indicates that there may have been other similar cases that would not have come to autopsy (as hospital autopsies are in decline). With vCJD apparently on the decline, interest in sCJD may also wane and there may be less interest in notifying cases to the NCJDSU. Education is important as it alerts clinicians to the clinical phenotype and the appropriate procedures. Methods of increasing awareness amongst these clinicians

need to be balanced with the time and effort required to enhance referral of a potentially small number of cases. To include all general physicians and psychiatrists on the yearly reminder circulation list is logistically a demanding process. There are other ways of "advertising" the NCJDSU, which may include publications in the scientific and medical press, presentations at medical conferences and the internet (see www.cjd.ed.ac.uk).

Possible sCJD: are there ways of improving diagnostic certainty in this group?

The reason why a case remains classified with the uncertain label of Possible sCJD is because of a lack of supportive investigations (a characteristic EEG or a positive CSF14-3-3), a failure to make an alternative diagnosis and the absence of an autopsy. Assessing the cases classified as Possible has enabled some of the shortfalls of the diagnostic process to be examined. Every process of this nature should include feedback into the original system to suggest methods of improvement and a re-evaluation after a period of time has elapsed (i.e. completion of the audit process).

Shortfalls in the use of diagnostic tests

CSF 14-3-3 has been very useful in enabling many cases to be classified as Probable sCJD in whom the EEG was not typical. When employed in the correct clinical context 14-3-3 shows a high sensitivity and specificity for sCJD[161;232]. Over half of the patients finally classified as Possible were referred to the NCJDSU before the advent of CSF 14-3-3. In ten cases referred after the development of the test however, it was overlooked as an aid to diagnosis. The advent of CSF 14-3-3 test, however, does not

correlate with a decrease in the number of patients classified as Possible per year or the proportion of total referrals classed as Possible. Between two and 13 cases a year have been finally classified as Possible sCJD throughout the study period. Overall referral numbers have increased whereas autopsy rates have decreased by 20 per cent over the past seven years (see Figure 3.23) leading to less Definite cases. There is a trend for the proportion of cases in the Probable sCJD group to have increased and this may reflect both increased certainty in diagnosis (Possible cases becoming Probable) provided by CSF 14-3-3 and the decreased number of autopsies carried out (less Definite cases). The lack of decrease in the number of Possible cases may reflect an increased tendency to refer cases where the diagnosis is uncertain. In addition the decline in autopsy rates main mean that more cases are left as Possible only. Only six of the 59 Possible cases had CSF 14-3-3 performed. This test could be used more frequently in the future to enhance diagnostic accuracy.

The EEG may have to be repeated on a number of occasions for a characteristic appearance to develop and it is clear that, in the majority of patients studied here, multiple EEGs were not recorded. Other factors are also known to increase the sensitivity of the EEG including later timing of the recording[215], older age and a MM codon 129 genotype [87;233]. Possible cases in this study have a mean age of 73 years (older than that typically seen in sCJD) and a mean duration of illness of five months. Genotype data was only known in a small minority making it difficult to meaningfully comment on this amongst these cases. Forty patients (68%) classified finally as Possible sCJD cases had an EEG recording performed in the second half of the illness but less than a quarter in the final month. Encouraging an appropriate use of the EEG (repeatedly and at a late stage in the illness) is important if it is to continue to be regarded as a useful diagnostic test.

Underreporting amongst Possible cases

In just under one half of Possible cases the NCJDSU was not notified about the patient until after they had died. If a suspected case is notified to the NCJDSU in life then advice can be given about investigating appropriately (e.g. send CSF for 14-3-3, repeat EEG recordings). If a visit is made to see the patient by a NCJDSU doctor then information regarding the role of the autopsy in diagnosis can be given. Approximately 60 per cent of Probable or Definite sCJD cases were assessed by a NCJDSU doctor over the last six years compared with 48 per cent of cases with a final classification of Possible (NCJDSU, unpublished data). This may not just reflect the direct involvement of the NCJDSU in improving diagnostic certainty but also the experience of the referring clinicians (i.e. referral is more likely to occur in clinicians familiar with procedures and therefore more likely to investigate appropriately anyway). In addition, clinicians may be less likely to refer patients if they are not confident of the diagnosis and they may not appreciate the need to refer uncertain cases. It is important that the referral of cases where there is diagnostic doubt is encouraged.

Re-evaluating aspects of the diagnostic criteria

It has been suggested that there may be a role in the case definition of sCJD for the appearances of high signal in the caudate head and putamen bilaterally seen in between 50-60% on the cerebral MRI scan. One of the arguments against this is that these appearances may be seen in other conditions* and therefore may compromise specificity. Unfortunately only a small number of MRI scans (15%) were available for

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* Wilson's disease, hypoxic encephalopathy, carbon monoxide poisoning, hepatic encephalopathy.

review from the Possible cases. Of these, three (33%) showed the characteristic high signal change in the caudate head and putamen. It would be crucial to view larger number of MRI scans on such patients in the future before a decision could be made regarding the inclusion of this extra factor in diagnostic criteria. Retrospectively changing the criteria to incorporate the MRI scan as a factor that could define a Probable case would only have resulted in a further three cases being classified as Probable on the basis of currently available information.

Another point to consider is a purely clinical one and has arisen largely from the observation amongst the non-CJD cases that none had a duration of illness of less than four months. In the Possible group 27 per cent of the cases had a disease duration of three months or less associated with myoclonus. The findings in this study indicate that this may be an area for further consideration possibly by reviewing Europe wide cases to see if the same level of specificity for sCJD occurs with these very short duration dementias elsewhere. Clearly this would only enable reclassification of cases after death if this factor were considered specific enough to enable a classification of Probable CJD to be made.

Cases that were thought to have sCJD but had an alternative diagnosis proven at autopsy

These cases are interesting because they provide an insight into the extent of the differential diagnosis when considering a patient with suspected sCJD. An understanding of this area is particularly important in view of the fact that autopsy rates are declining, highlighting the need for accuracy in clinical diagnosis wherever

possible. This study has demonstrated that other neurodegenerative conditions (especially Alzheimer's disease) and paraneoplastic/neoplastic disorders are most likely to cause significant diagnostic confusion. Despite this it is noteworthy that of all the cases referred to the NCJDSU since 1990 only two cases who were classified as Probable sCJD in life went on to have an alternative diagnosis proven at autopsy (one had a paraneoplastic disorder with a positive 14-3-3 and the second, who was diagnosed in 2003 and therefore not included in the results of this study, had an ischaemic/anoxic encephalopathy and a positive EEG).

A case where an alternative diagnosis was proven at autopsy but evidence of sCJD was found upon review

An important lesson regarding the interplay of clinical and neuropathological expertise is learnt with the described case of the 84 year old gentleman who, after an illness clinically typical of sCJD, had an autopsy which yielded a diagnosis of Alzheimer's disease. Only in the course of this study (some ten years after the patients death) was the neuropathology reviewed in light of the overwhelmingly characteristic clinical picture. The subsequent finding of a dual pathology (of sCJD and Alzheimer's disease) highlights the need for good communication between clinicians and neuropathologists as well as emphasising that (especially in the elderly) more than one pathology may occur[121-123;234]. In previously reported cases where both sCJD and Alzheimer's disease were found at autopsy clinical features varied. One report details a slowly progressive illness over five years with a rapid exacerbation of symptoms in the last three months[123] whilst another describes akinetic mutism two months after the initial symptoms[235].

More advanced neuropathological techniques are now available for detecting PrP^{Sc} and it is possible that other similar cases may exist that have been overlooked in the past. Clearly the detection of such a case many years after death has implications for the family members and care needs to be taken in communicating such a result back to unsuspecting relatives. Such cases are likely to be rare however and in this study a review of other "non-cases" revealed two further cases with an autopsy diagnosis of Alzheimer's disease and a duration of illness of less than six months. A detailed neuropathological review in these additional two cases failed to reveal any evidence of PrP^{Sc}. An interesting further study may be to review the neuropathology of other cases throughout Europe with a short duration of illness referred as suspect sCJD but given an alternative diagnosis at autopsy.

There are no other cases known to the NCJDSU with a dementing illness lasting three months or less with a diagnosis other than CJD. This implies that a feature *specific* to sCJD, at least in those cases referred to NCJDSU, may be the incredible rapidity of decline often observed. It is possible, however, that this may be an artefact of the cases referred to the NCJDSU, i.e that rapidly progressive dementias of other cause may be recognised and diagnosed by local clinicians without referral to the NCJDSU.

Distinguishing other diseases from sCJD

Has this study brought us any further forward in being able to differentiate other conditions from sCJD? On the whole in non cases disease duration was considerably longer than that witnessed in sCJD although on an individual basis there was overlap between the two groups. In patients referred to the NCJDSU with an illness duration of less than three months, sCJD is found unanimously at autopsy.

Undoubtedly at times the presence of myoclonus and a rapidly progressive dementia may be misleading, pointing towards CJD when the diagnosis is an alternative condition[91]. As previously described, the clinical diagnostic criteria are accurate in terms of filtering out non-CJD cases (i.e. a Probable diagnosis carries with it a high specificity) and therefore it is better that the initial referrals are relatively broad to decrease the chance of cases being missed. There are no cases in the cohort of non cases studied here with myoclonus, a rapidly progressive dementia and a typical EEG.

It is important not to discourage the referral of longer duration cases that are more likely to have Alzheimer's (AD) or another condition. This work indicates that among this group there may be unusual cases of sCJD. This study has not identified features that clearly distinguish long duration sCJD from alternative diagnoses such as AD. This emphasises the need for an autopsy to be sure of the diagnosis. Clinical diagnostic accuracy for AD rests at between 62.5% and 100%[236;237] and previous studies have highlighted several factors as potentially alerting a clinician to an incorrect diagnosis of AD (including focal neurological signs and extrapyramidal features)[238]. Cases that were labelled in life as having AD and went onto autopsy have on occasion had coexistent CJD but there has not been a high prevalence of undiagnosed sCJD[234]. Some of the long duration cases in this study had an autopsy because of features that were unusual (e.g. young age or rapid terminal decline). There may however be cases where these unusual features do not occur, are labelled as AD and do not have an autopsy. There has been a decline, since 1996, in the number of non-cases referred to the NCJDSU who had Alzheimer's disease (AD) proven at autopsy. This may indicate that some long duration sCJD cases are being missed as in this study cases have been shown to arise from the premortem cohort of "suspected AD". It also may mean, however, that there is a greater awareness of

somewhat unusual AD (e.g. with myoclonus) leading to more accurate diagnosis of AD.

CONCLUSIONS

This study has demonstrated that sporadic Creutzfeldt-Jakob Disease manifests in clinically distinct ways. By describing cases observed over a twelve year period it has provided a comprehensive review of the phenotypic spectrum. Unusual cases may cause problems in diagnosis if rigid ideas regarding disease presentation and progression are adhered to. It is important that those involved in the field of CJD surveillance encourage the referral of unusual cases and continue to be involved in maintaining a high level of awareness regarding the disease and its different manifestations. Methods to increase the representativeness of surveillance are important if an understanding of the patterns of disease is to be complete.

This study has identified circumstances where weaknesses in case detection may exist. It has highlighted methods of enhancing future diagnostic accuracy by the appropriate use of diagnostic tests such as the EEG, which should be repeated late into the illness. Long duration cases may pose particular problems in diagnosis, both by not exhibiting the rapidity of decline so striking in many cases of the disease and also because diagnostic tests have low positive yields. It is important that sCJD is thought of in unusual dementias, and it is hoped that the NCJDSU is approached readily for advice. For their part, surveillance neurologists must encourage the referral of unsual cases and keep an open mind to phenotypic variations, especially in cases with a longer illness duration. This may increase the rate of autopsy examination in such cases, which may be the only way to make a positive diagnosis.

Prion diseases are particularly devastating conditions. By active and accurate surveillance it is hoped that more may be understood regarding pathogenesis

and susceptibility, with the long term aim of providing effective treatments and/or preventative measures.

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Appendix 1: Surveillance case definition for Variant CJD

I	A	Progressive neuropsychiatric disorder
	B	Duration of illness > 6 months
	C	Routine investigations do not suggest another diagnosis
	D	No history of potential iatrogenic exposure
	E	No evidence of a familial form of CJD
II	A	Early psychiatric symptoms[1]
	B	Persistent painful sensory symptoms[2]
	C	Ataxia
	D	Myoclonus or chorea or dystonia
	E	Dementia
III	A	EEG does not show the typcal appearance of sporadic CJD[3] (or no EEG performed)
	B	MRI brain shows blateral symmetrical pulvinar high signal[4]
IV	A	Positive tonsil biopsy

DEFINITE IA **and** neuropathological confirmation of vCJD

PROBABLE I **and** 4/5 of II **and** IIIA **and** IIIB

OR

I **and** IVA

POSSIBLE I and 4/5 of II and IIIA

---

[1] depression, anxiety, apathy, withdrawal, delusions
[2] this includes both frank pain and/or dysasesthesia
[3] generalised triphasic periodic complexes at approximately one per second
[4] relative to the signal intensity of other deep grey matter nuclei and cortical grey matter

Appendix 2: EEG classification used by the NCJDSU

I Normal

II Non specific

Non-specific deterioration in normal background activity
Non-specific excessive slow wave activity
Non-specific excessive fast wave activity

III Suggestive

General deterioration in/loss of normal background
Intermittent bi/tri phasic discharges similar to those seen in classical CJD records
BUT

a) occurring in bursts of only relatively short duration (<15 seconds) AND either b) or c) or both
b) not being truly generalised and synchronous
c) without true periodicity

IV Highly Suggestive

Generalised deterioration in /loss of normal background
Intermittent bi/tri phasic discharges similar to those seen in classical CJD records
Being truly periodic and generalised at times
BUT
Either a) or b)

a) occurring in bursts of only relatively short duration (<15 seconds) and occupying less than a quarter of the record
b) not being truly generalised and synchronous in all portions of the record where they occurred

V Typical

General deterioration in/loss of normal background
Truly periodic generalised synchronous bi/tri phasic discharges
Occuring throughout the whole record or at least one quarter of it and in relatively long segments (15 seconds at a minimum)

Appendix 3: Patient review and examination forms, pre- and post-1997

Patient Review and Examination Form (Post-1997)

1. Identification information		**Id number**	☐☐☐☐☐
1.1	What is the patient's name:	First name	_____
		Surname	_____
1.2	Name of the patient's consultant:		_____
1.3	Hospital address Name of hospital		_____
		Street	_____
		Town	_____
		Postcode	_____
		Telephone number	_____
	Patient's hospital record number		_____
1.4	Who is the patient's G.P.? Surname+initial		_____
1.5	G.P.'s address	Street	_____
		Town	_____
		Postcode	_____
		Phone number	_____
1.6	Patient's NHS number: old:		☐☐☐☐☐☐☐☐☐☐
		new:	☐☐☐☐☐☐☐☐☐☐
1.7	Date of examination (dd/mm/yyyy):		____/____/_____
1.8	Examination performed by:		_____

2. Clinical history (continued)

3. State of patient at admission/first examination by a neurologist

3.1 General appearance:

3.2 Mental state/speech functions:

3.3 Cranial nerves:

3.4 Motor system:

Involuntary movements:

3.5 Sensory system:

3.6 Reflexes:

primitive:

tendon:

plantar:

3.7 Cerebellar function/coordination:

3.8 General examination:

4. Previous medical history

Complete this section of the form using the medical notes available. All questions refer to the patient's history prior to the onset of the current illness.

4.1	Does the patient have a record of previous hospital admissions unrelated to the present illness? (1=yes, 2=no) (*If yes*), on how many occasions has the patient been admitted to hospital? (88=not applicable) (*If yes*) record the hospital's name, the date(s) of admission and the reason(s) for the admission?	☐ ☐☐ _____ _____ _____ _____ _____ _____ _____ _____ _____ _____ _____ _____ _____ _____ _____ _____

4.2	Has the patient ever had a diagnosis of inflammatory bowel disease? (1=yes, 2=no) (*If yes*) record date of first diagnosis (dd/mm/yyyy)	 _____/_____/_____
4.3	Has the patient ever been diagnosed as diabetic? (1=yes, 2=no) (*If yes*) record date of first diagnosis (dd/mm/yyyy) (*If yes*) has the patient received insulin? (1=yes, 2=no) (*If patient has received insulin*) record date of first and last prescription (dd/mm/yyyy)	 _____/_____/_____ _____/_____/_____First _____/_____/_____Last
4.4	Has the patient ever undergone surgery requiring a general anaesthetic? (1=yes, 2=no) (*If yes*) record the date of the surgery, the procedure(s) performed, and the name of the hospital where the procedure(s) took place.	 _____ _____ _____ _____
4.5	Has the patient ever undergone surgery without general anaesthetic? (1=yes, 2=no) (*If yes*) record the date of the surgery, the procedure(s) performed, and the name of the hospital where the procedure(s) took place.	 _____ _____ _____ _____ _____
4.6	On how many occasions in all has the patient undergone surgery (with or without general anaesthetic)?	

4.7	Has the patient ever received an organ transplant (including corneal or bone marrow transplant)? (1=yes, 2=no) (*If yes*) record the date, organ received and name of hospital.	☐ _____ _____ _____ _____ _____
4.8	Has the patient ever received blood or blood products? (1=yes, 2=no) (*If yes*) record the date, type of product, name of hospital and reason.	_____ _____ _____ _____ _____ _____
4.9	Has the patient ever received a treatment involving a course of injections (excluding any treatments related to the current illness)? (1=yes, 2=no) (*If yes*) record the year of the treatment, the medication(s) involved and the reason.	_____ _____ _____ _____ _____ _____

4.10	Non-injectable treatments lasting more than 4 weeks: record the start date of the treatment, the duration, the medicine and the reason for the treatment	
1.		
2.		
3.		
4.		
5.		
6.		
7.		
8.		
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10.		
11.		
12.		
13.		
14.		
15.		
16.		
17.		
18.		
19.		
20.		
4.11	**Has the subject ever been exposed to one of the medications of bovine origin withdrawn in 1990?** (1=yes, 2=no)	☐

5. Examination of the patient

5.1 General appearance

Bedbound

NG/PEG

Catheterised

Akinetic mute

Posture

Myoclonus

Startle

Other involuntary movements

5.2 Mental state/speech functions

Best motor response

Best verbal response

Eye opening

5.3 Cranial nerves

Fields/response to menace

Pupils

EOMs/doll's eyes

Corneal reflex

Gag reflex

Facial weakness

5.4 Motor system

Tone

Power

Wasting

5.5 Sensory system

5.6 Reflexes

- Primitive Grasp

Palmomental

Pout

Rooting

- Tendon reflexes (including jaw jerk)

- Plantar

5.7 Cerebellar function/coordination

5.8 General examination

6.	**Recording/coding of history and examination**	
6.1	What were the first symptoms of illness noted by the patient or their family?	_____ _____
	When did these symptoms first occur? (dd/mm/yyyy)	____/____/_____
6.2	When did the patient first seek medical attention for the illness? (dd/mm/yyyy)	____/____/_____
6.3	When was the patient first referred to a neurologist? (dd/mm/yyyy)	____/____/_____
6.4	When was the patient first admitted for the current illness? (dd/mm/yyyy)	____/____/_____
6.5	Since the start of the illness, until the current time, has the patient exhibited the following neurological symptoms/signs: (*if yes record the date of the first appearance of the symptom/sign*)	**Coding:** 1=yes, 2=no, 3=unsure, 9=not able to ascertain. If yes, but date unknown record as 09/09/0909
	rapidly progressive dementia	____/____/_____
	cerebellar signs	____/____/_____
	visual signs	____/____/_____
	oculomotor signs	____/____/_____
	pyramidal signs	____/____/_____
	extrapyramidal signs	____/____/_____
	primitive reflexes	____/____/_____
	seizures	____/____/_____
	myoclonus	____/____/_____
	other involuntary movements	____/____/_____
	headache	____/____/_____
	pain	____/____/_____
	other sensory disturbances	____/____/_____

6.5	(continued) vertigo/dizziness	☐ ____/____/_____
	pseudobulbar signs	☐ ____/____/_____
	neurogenic muscle wasting	☐ ____/____/_____
	akinetic mutism	____/____/_____
6.6	Since the start of the illness, until now, has the patient exhibited the following clinical symptoms/ signs: (*if yes record the date of the first appearance of the symptom/sign*)	**Coding:** 1=yes, 2=no, 3=unsure, 9=not able to ascertain. If yes, but date unknown record as 09/09/0909
	gait disturbances	
	speech disturbances	____/____/_____
	visual disturbances	____/____/_____
	forgetfulness	____/____/_____
6.7	Since the start of the illness, has the patient been seen by a psychiatrist? (1=yes, 2=no)	____/____/_____
	(*If yes*) record the date of the first consultation (dd/mm/yyyy)	
6.8	Since the start of the illness until now, has the patient exhibited the following psychiatric symptoms/signs: (*if yes record the date of the first appearance of the symptom/sign*)	____/____/_____ **Coding:** 1=yes, 2=no, 3=unsure, 9=not able to ascertain. If yes, but date unknown record as 09/09/0909
	clinical depression	____/____/_____
	social withdrawal	____/____/_____
	low mood and apathy	____/____/_____
	anxiety	____/____/_____
	delusions	____/____/_____
	hallucinations	____/____/_____
	aggression	____/____/_____

7.	**Investigations**	
7.1	Has the patient undergone an EEG? (1=yes, 2=no)	☐
	(*If yes*), on how many occasions?	☐☐
	(*If yes*), record date of most recent EEG (dd/mm/yyyy)	____/____/_____
	Are EEG records/copies available in the Unit? (1=yes all, 2=yes some, 3=no, 8=not applicable)	☐
	Have the EEGs been examined by a Unit staff member? (1=yes all, 2=yes some, 3=no, 8=not applicable)	☐
7.2	Has the patient recorded an EEG characteristic of CJD (generalized triphasic periodic complexes with frequency about 1/s)?(1=yes, confirmed by Unit staff, 2=yes, reported by local staff, EEG not available for confirmation by Unit staff, 3=no, 8=no EEG performed)	☐
	What was the basis for the classification of the EEG? (1=informal, 2=Oxford criteria, 3=Gottingen criteria, 4="WHO" criteria, 8= no EEG performed)	☐
	(*If yes*) record the date on which the first characteristic EEG was recorded (dd/mm/yyyy)	____/____/_____
7.3	Has the patient ever had a CT scan? (1=yes, 2=no)	☐
	(*If yes*), on how many occasions?	☐☐
	(*If yes*), record date of most recent scan (dd/mm/yyyy)	____/____/_____
	Are CT scan results available in the Unit (1=yes all, 2=yes some, 3=no, 8=not applicable)	☐
	Have the CT scans been examined by a Unit staff member? (1=yes all, 2=yes some, 3=no, 8=not applicable)	☐☐
7.4	Has the patient ever had an abnormal CT scan? (1=yes, confirmed by Unit staff, 2=yes, reported by local staff, scan not available for confirmation by Unit staff, 3=no, 8=no scans performed)	____/____/_____
	(*If yes*) record the date on which the first abnormal scan was performed (dd/mm/yyyy)	_____
	(*If yes*) specify what abnormalities have been observed	_____

7.5	Has the patient ever had an MRI scan? (1=yes, 2=no)	☐
	(*If yes*), on how many occasions?	☐☐
	(*If yes*), record date of most recent scan (dd/mm/yyyy)	____/____/_____
	Are MRI scan results available in the Unit (1=yes all, 2=yes some, 3=no, 8=not applicable)	☐
	Have the MRI scans been examined by a Unit staff member? (1=yes all, 2=yes some, 3=no, 8=not applicable)	☐
7.6	Has the patient ever had an abnormal scan? (1=yes, confirmed by Unit staff, 2=yes, reported by local staff, scan not available for confirmation by Unit staff, 3=no, 8=no scans performed)	
	(*If yes*) record the date on which the first abnormal scan was performed (dd/mm/yyyy)	☐ ____/____/_____
	(*If yes*) specify what abnormalities have been observed	_____ _____ _____ _____
7.7	(*If an abnormal MRI scan has been reported by someone outside the unit*) who reported the abnormal scan?	
	Name: _____	
	Address:_____	
	_____	

7.8	CSF findings (fill coding boxes with 8s if test results are not available)		
	Date of first CSF collection (dd/mm/yyyy)		____/____/_____
	Results:	protein	. mg/L
		glucose	. mmol/L
		cell count	count/mm^3
		14-3-3	(1=negative, 2=equivocal, 3=positive)
		NSE	. ng/ml
		S100b	. ng/ml
		tau	pg/ml
	Ig oligoclonal bands in:	CSF	1=positive, 2=negative
		blood	1=positive, 2=negative
	Date of second CSF collection (dd/mm/yyyy)		____/____/_____
	Results:	protein	. mg/L
		glucose	. mmol/L
		cell count	count/mm^3
		14-3-3	(1=negative, 2=equivocal, 3=positive)
		NSE	. ng/ml
		S100b	. ng/ml
		tau	pg/ml
	Ig oligoclonal bands in:	CSF	1=positive, 2=negative
		blood	1=positive, 2=negative

7.9	Has the patient had any abnormal liver function test results recorded? (1=yes, 2=no) (*If yes*) specify abnormality and give date of first abnormal test:_____ _____ _____	☐ ____/____/_____
7.10	Does the patient have any abnormalities on other routine biochemical/haematological investigations? (1=yes, 2=no) (*If yes*) give describe the investigation(s) and the abnormalities	☐

_____

_____

_____

_____

_____

7.11	Has the patient undergone a brain biopsy? (1=yes, 2=no)	☐
	(*If yes*) what was the result? (1=no evidence of spongiform change, 2=spongiform change without florid plaques, 3=spongiform change with florid plaques, 4=result not yet available, 8=no biopsy performed)	☐
	Name of neuropathologist:	_____
7.12	Has the patient undergone a tonsil biopsy? (1=yes, 2=no)	
	(*If yes*) what was the result? (1=no evidence of PrP immunostaining, 2=equivocal, 3=PrP positive, 4=result not yet available, 8=no biospy performed)	☐
		_____
8.	**Specimens collected**	1=yes, 2=no Quantity (mls)
8.1	Blood: frozen for general use	☐ ☐☐
	separated and frozen for transmission studies	☐ ☐☐
8.2	Urine	☐ ☐☐
8.3	CSF	☐ ☐
9.	**Patient classification**	
9.1	On the basis of the available information, what is the classification of the patient? (1.0=definite CJD, 2.0=probable CJD, 3.0=possible CJD, 4.1=diagnosis unclear, 4.2=CJD thought unlikely, 4.3=definitely not CJD, 5=GSS)	
	(*If patient is classified as at least possible CJD or GSS*) which category of disease is suspected? (S=sporadic CJD, N=nvCJD, F=familial CJD, I=iatrogenic CJD, G=GSS, 8=not applicable)	

Pre-1997 clinical proforma

CLINICAL HISTORY

EXAMINATION ON ADMISSION

1. General appearance:

2. Mental state/speech functions:

3. Cranial nerves:

4. Motor system:

5. Reflexes:

6. Sensory system:

7. General examination:

REVIEW OF PROGRESSION OF PHYSICAL SIGNS

EXAMINATION

1. General appearance:

2. Mental state/speech functions:

3. Cranial nerves:

4. Motor system:

5. Reflexes:

6. Sensory system:

7. General examination:

INVESTIGATIONS

a) Abnormalities on routine biochemical/haematological investigation:

b) LFT's

c) CSF:

d) EEG results:

e) CT scan:

f) MRI scan:

e) Other investigations:

TREATMENT

OUTCOME

a) Date of death:

Place of death:

Cause of death:

b) Review of clinical course:

c) EEG progression:

d) Abnormalities in other investigations:

e) Post-mortem: Yes/No

Histology

f) Blood taken for genetic studies? Yes/No

Analysing Centre:

CLASSIFICATION

			Present	Absent
1.	Rapidly progressive dementia:			
2.	a)	Myoclonus		
	b)	Cortical blindness		
	c)	Pyramidal/extra-pyramidal/ cerebellar signs		
	d)	Akinetic mutism		
	e)	Early onset of neurogenic muscle wasting		
	f)	Characteristic EEG		
3.	Histology:			

Classification

1. CJD
   - Definite
   - Probable
   - Possible
2. Other